14th Congress of the

INTERNATIONAL SOCIETY FOR AUTONOMIC NEUROSCIENCE

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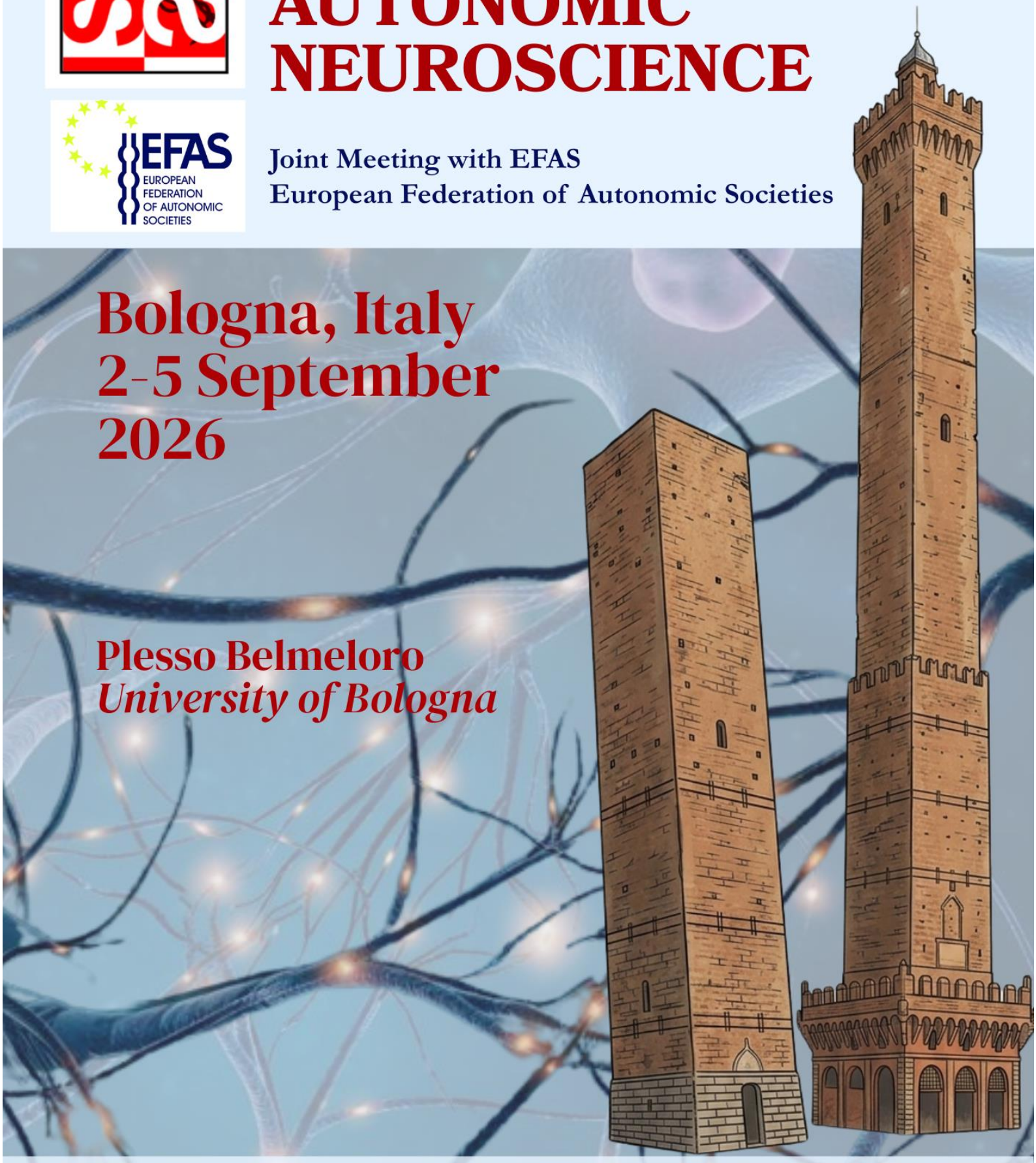

Bologna, Italy
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Plesso Belmeloro
University of Bologna

ABSTRACT BOOK

Avenue media
Conference & Expo

1. KEYNOTE LECTURES

K1. Sympathetic Neuroimmunity In Obesity - Ana Domingos

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The brain controls adiposity via a direct connection between peripheral sympathetic neurons and adipocytes. Further, we found this neuro-adipose junction to drive lipolysis via norepinephrine (NE) signaling which is necessary and sufficient for fat mass reduction (1). Further, we reported the discovery of Sympathetic neuron-Associated Macrophages (SAMs) that directly regulate the extracellular availability of norepinephrine (NE) and identified the molecular mechanism by which SAMs import and metabolize norepinephrine (NE). Abrogation of the mechanism for the uptake of NE by SAMs increases NE availability, which in turn promotes thermogenesis and browning, and long-term amelioration of obesity independently of food intake (2). As obesity is a chronic inflammatory state, we will discuss additional neuroimmune mechanisms that link inflammation to SNS neuronal function, and leptin resistance (3).

K2. Sleep And The Autonomic Nervous System: Clinical Insights And Pathophysiology - Pietro Cortelli

Alma Mater Studiorum, University of Bologna - Alma Mater Studiorum, Bologna, Italy

The central autonomic network consists of interconnected areas distributed throughout the neuraxis. These areas not only control the activity of the preganglionic neurons but also participate in coordination of autonomic with other homeostatic responses including respiration, arousal, and response to stress. These areas include the anterior cingulate and insular cortices, amygdala, periaqueductal gray, pedunculopontine nucleus, parabrachial nuclear complex, nucleus of solitary tract, ventrolateral medullary reticular formation, and rostral ventromedial medulla and raphe nuclei. The activity of neurons in these regions is regulated in a state-dependent manner during the sleep-wake cycle providing for changes in cardiovascular and respiratory functions during these states. Understanding of the functional organization of these autonomic structures is therefore of relevance to interpret cardiovascular, respiratory and other autonomic manifestation during normal sleep and in neurological disorders.

Indeed, sleep itself may be considered one of the most highly integrated autonomic functions at the forebrain diencephalic level, where the behavioural and homeostatic integration occurs being closely and bidirectionally interconnected with the others hierarchical levels.

Sleep and autonomic regulation are closely interconnected through a bidirectional relationship. Sleep profoundly influences blood pressure, heart rate, ventilation, and autonomic reflex function, while sleep disorders can both cause and be associated with clinically significant autonomic dysfunction. Conditions such as fatal familial insomnia, congenital central hypoventilation syndrome, obstructive sleep apnea, narcolepsy type 1, and REM sleep behavior disorder are characterized by clinically relevant abnormalities in cardiovascular and respiratory autonomic control. These autonomic disturbances adversely affect the prognosis of the underlying sleep disorder and may increase the risk of developing other chronic diseases or experiencing life-threatening events. Recent research has highlighted the clinical importance of nocturnal blood pressure phenotypes, blood pressure variability, and standardized autonomic function testing, underscoring their growing role in the evaluation and management of patients with sleep disorders.

K3. Cancer Neuroscience: The Autonomic Nervous System Regulates Cancer Progression And Treatment Response - Erica Sloan

Monash University, Drug Discovery Biology, Parkville, Australia

Solid tumours develop within local microenvironments embedded in a whole-body neural regulatory network. Through this network, the autonomic nervous system translates host physiology into tissue signals that shape cancer progression and treatment response. Using preclinical models of breast cancer, we show that sympathetic signalling acts across multiple timescales. Acute noradrenergic signalling regulates tumour cell invasion, vascular function and anti-tumour immunity. With sustained activation, these effects accumulate to promote metastatic dissemination. Over longer timescales, physiological stressors and cytotoxic therapy remodel sympathetic innervation itself. Anthracycline chemotherapy induces tumour-cell production of nerve growth factor, increasing sympathetic innervation and adrenergic signalling within surviving tumours and limiting control of metastatic disease. Disrupting sympathetic signalling improves treatment response, consistent with clinical evidence linking β-adrenergic blockade to reduced metastatic relapse in defined treatment contexts. These findings identify the autonomic nervous system as a dynamic, plastic regulator of cancer progression and a potential therapeutic target.

K4. Immunoregulation By Sympathetic Nerves: Can Neutrophils Be Selectively Targeted? - Alexandre Steiner

Universidade de Sao Paulo, Instituto de Ciencias Biomedicas, Sao Paulo, Brazil

The nervous system plays an important role in regulating immune function. In this talk, evidence for the role of the sympathetic nervous system in immunity will first be reviewed from a historical perspective, followed by a discussion of recent findings on the function of the greater splanchnic nerve in a rat model of E. coli-induced septic peritonitis.

Bilateral ablation of the greater splanchnic nerve (splanchnicectomy; SplancX) dramatically improved bacterial clearance in this model, reducing bacterial burden by 96% in the peritoneum and by 92% in the spleen. This major effect was not mediated by the afferent (sensory) fibers of the nerve, strongly suggesting that it is mediated by its efferent sympathetic fibers. Further experimentation pointed to the nerve branch supplying the adrenal gland as particularly important for this immunoregulatory mechanism.

The enhanced bacterial clearance in rats subjected to SplancX could not be explained by changes in macrophage function, in the cytokine network, or in the recruitment of immune cells to the sites of infection. Instead, single-cell RNA sequencing revealed that SplancX selectively reshaped neutrophil functional states, a specificity that had not been predicted based on previous findings from aseptic models of systemic inflammation. Whereas sham-operated infected rats exhibited a substantial population of quiescent neutrophils with immunosuppressive characteristics, SplancX shifted this population toward activated neutrophil subsets with a microbicidal transcriptional signature.

Looking ahead, these novel findings open avenues for exploring sympathetic nerves as targets for precision medicine in subgroups of patients with life-threatening infections (sepsis).

2. SYMPOSIA

1ST SYMPOSIUM - CHEMOREFLEX AND AUTONOMIC DYSFUNCTION: FROM MECHANISMS TO THERAPEUTIC TARGETS ACROSS DISEASES

TOPIC 01. Cardiovascular Autonomic Regulation In Health And Disease

S.1 The Chemoreflex Axis In HFpEF: Peripheral Triggers, Brainstem Astrocytes, And Glutamate-driven Cardiorespiratory Instability

Rodrigo Del Rio (1)

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Heart failure with preserved ejection fraction (HFpEF) is a health problem worldwide in which autonomic imbalance, and respiratory instability interact to worsen cardiovascular outcomes. Exaggerated chemoreflex activation has emerged as an important contributor to sympathetic overactivation, disordered breathing, exercise intolerance, and cardiac dysfunction in HFpEF. However, the mechanisms linking peripheral chemoreceptor activation to central chemoreflex remodeling remain incompletely understood.

Experimental evidence supports a model in which HFpEF involves maladaptive remodeling of a peripheral-central chemoreflex axis. At the peripheral level, carotid body hyperactivity provides sustained excitatory input to brainstem respiratory-autonomic circuits, promoting central chemoreflex potentiation, ventilatory instability, and adverse cardiac loading. At the central level, the retrotrapezoid nucleus (RTN), a key brainstem chemosensory region, represents a critical site where heart failure reshapes neuron-glia signaling. In a non-ischemic heart failure model characterized by preserved systolic function, diastolic dysfunction, autonomic imbalance, and breathing instability, heart failure was associated with selective loss of astrocytic glutamate transporter-1 (GLT-1) in the RTN. This deficit impaired extracellular glutamate homeostasis, leading to glutamate spillover, enhanced RTN central chemoreceptor neuron excitability, exaggerated hypercapnic ventilatory responses, and unstable breathing patterns.

Selective restoration of GLT-1 expression in RTN astrocytes normalized extracellular glutamate levels, reduced central chemoreceptor neuron hyperexcitability, stabilized breathing, improved cardiac autonomic balance, and attenuated load-dependent diastolic dysfunction. Complementary pharmacological experiments using systemic riluzole, an FDA-approved glutamate-modulating drug, reduced RTN glutamate accumulation and attenuated respiratory instability, supporting the therapeutic tractability of this pathway while highlighting the need for more spatially and cell-specific approaches.

Importantly, these interventions improved physiology without reversing structural cardiac remodeling, suggesting that central chemoreflex circuits can modify functional disease expression beyond primary cardiac pathology.

Together, these findings support the concept that carotid body hyperactivity and RTN astrocytic glutamate dysregulation cooperate to sustain chemoreflex hyperactivity in HFpEF. This peripheral-central chemoreflex axis provides a mechanistic framework linking respiratory control, autonomic imbalance, and cardiac dysfunction, and may reveal new therapeutic opportunities to reduce cardiorespiratory instability in HFpEF.

S.2 Chemoreflex Adaptations in Metabolic Disease and Obesity

Silvia Conde (1)

(1) iNOVA4Health, NOVA Medical School, University NOVA Lisboa, Portugal

The carotid bodies (CBs) are classically recognized as peripheral chemosensors that regulate respiratory and cardiovascular responses to changes in arterial oxygen. Increasing evidence, however, indicates that CB activity is profoundly influenced by metabolic status and that its dysregulation may contribute to the pathophysiology of obesity and metabolic diseases.
In this talk, I will discuss evidence showing that metabolic dysfunction is associated with increased CB activity and enhanced chemoreflex drive. This heightened chemosensory activity promotes sustained changes in respiratory control and sympathetic outflow, linking peripheral chemosensory signaling to the autonomic alterations characteristic of metabolic disease. Importantly, the consequences of CB activation extend beyond respiratory and cardiovascular regulation. Through autonomic pathways, CB activity can influence adipose tissue and liver function, providing potential mechanisms by which peripheral chemosensory signals contribute to the regulation of energy homeostasis and metabolic adaptation.
Using experimental models of obesity and metabolic dysfunction, we have investigated how CB activation shapes respiratory responses, sympathetic activity and adipose tissue and liver physiology. Our findings support a model in which metabolic stress enhances CB activity, increasing chemoreflex-mediated respiratory and sympathetic responses and altering autonomic control of liver and adipose tissue. This establishes the CB as a potential integrative sensor linking metabolic state to respiratory, autonomic and metabolic function.
Understanding how CB hyperactivity emerges in obesity, and how its downstream autonomic effects influence adipose tissue, may reveal new mechanisms underlying metabolic disease and identify the chemoreflex-CB axis as a potential theraputic target.

TOPIC 10. Development, Aging And Sex Differences In Autonomic Function

S.3 The Many Facets of the Carotid Body: From Hypertension to Sodium Intake

Débora Simões A. Colombari (1)

(1) School Of Dentistry, São Paulo State University (UNESP),

Several studies, including those from our laboratory, have shown that the carotid bodies (CB) play a role beyond respiratory regulation. We have demonstrated that CB are involved in mediating cardiorespiratory and autonomic responses to acute sodium overload, the development of renovascular hypertension, and, more recently, controlling water and sodium intake. Hypertonic sodium solution infusions increased carotid sinus nerve activity and induced sympathoexcitation and tachypnea, whereas CB removal attenuated the sympathoexcitatory response without affecting tachypnea. CB removal also impaired the development of renovascular hypertension, a secondary form of hypertension and highly dependent on increased levels of renin and angiotensin II. Preliminary data also demonstrated that CB are important for water intake and salt appetite (ingestion of hypertonic sodium solutions) induced by water deprivation, a common situation in humans and animal wildlife. Therefore, we will focus on the many facets of the CB's regulatory functions, apart from respiratory control, and how these are integrated.

TOPIC 01. Cardiovascular Autonomic Regulation In Health And Disease

S.4 Chemoreflex Sensitivity As A Therapeutic Target In Sleep Apnea And Heart Failure

Alberto Giannoni (1)

(1) Scuola Superiore Sant'Anna, University, Pisa, Italy

Abstract Enhanced chemoreflex sensitivity is a prevalent but heterogeneous feature of heart failure (HF) and sleep apnea. By amplifying ventilatory responses to small changes in arterial O_2 and CO_2, excessive chemoreflex gain increases ventilatory instability, promotes central apneas during wakefulness and sleep, and couples disordered breathing to sympathetic overactivity. In contemporary HF cohorts receiving guideline-directed therapy, combined hypoxic and hypercapnic hypersensitivity remains frequent, is associated with higher norepinephrine levels and 24-hour central apneas, and independently predicts adverse cardiovascular outcomes, particularly HF hospitalization. Thus, chemoreflex overactivity may represent a modifiable disease mechanism rather than a simple marker of severity.

Central and peripheral pathways may both be targeted. In the randomized, double-blind, placebo-controlled crossover BREATH study, the 5-HT_1A partial agonist buspirone reduced CO_2 chemosensitivity and decreased central apneas and oxygen desaturation. Experimental studies implicate purinergic P2X3 signalling in carotid-body afferents in respiratory and autonomic dysfunction in HF. However, gefapixant, a P2X3 receptor antagonist, did not reduce apnea severity in chemoreflex-dependent obstructive sleep apnea, illustrating the challenges of clinical translation.

The next step is physiology-guided precision therapy. Combining ventilatory chemoreflex testing with microneurographic assessment of muscle sympathetic nerve activity may distinguish ventilatory-predominant from autonomic-predominant hyperreflexia and identify patients most likely to benefit. Chemoreflex modulation should now be evaluated in phenotype-enriched trials using integrated respiratory, autonomic and cardiovascular endpoints.

TOPIC 11. Emerging Concepts And Novel Perspectives In Autonomic Neuroscience

O.1 Brainstem Respiratory Network Activity During The Hypoxic Ventilatory Response

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(1) Case Western Reserve University, Department of Medicine, Cleveland, United States - (2) Case Western Reserve University, Department of Mathematics, Applied Mathematics & Statistics, Cleveland, United States

Introduction: Hypoxia is transduced by carotid body (CB) chemoreceptors, whose input to the respiratory network evokes a stereotypical modulation of the breathing pattern known as the hypoxic ventilatory response (HVR). The HVR evoked by a brief hypoxic exposure is characterized by an acute phase wherein ventilation is augmented and a post-hypoxic phase in which ventilation is depressed below baseline. Dorsolateral pontine areas are necessary for the expression of the physiologic respiratory motor pattern. Similarly, dorsolateral and ventrolateral pontine areas are necessary for the respiratory chemoreflex. Yet, despite the established contributions of pontine areas to the control of breathing, we do not understand the circuit level mechanisms by which pontine areas modulate medullary neuronal activities. Here, we tested the hypothesis that CB stimulation modulates and reconfigures neuronal activity throughout the ponto-medullary respiratory network.

Methods: Experiments were performed in juvenile (P16-24), male Sprague-Dawley rats in situ. The respiratory motor pattern was recorded on phrenic, vagal and hypoglossal nerves. We simultaneously monitored the activities of ca. 100 respiratory neurons in the dorsolateral pons and medullary respiratory column using three 64-channel MEA probes. After 10 min of baseline activities, we stimulated the CBs via a bolus administration of NaCN (0.1mL, 0.1% w/v) allowing for at least a 5 min recovery between CB stimulations. MEA recordings were spike sorted using the Kilosort4 algorithm to identify single neuron firing patterns.

Results: At baseline, medullary neurons largely had bursting firing patterns that were highly correlated with the motor pattern, whereas pontine neurons fired tonically. Consistent with previous reports, CB stimulation evoked an excitation of on-going medullary neuronal activities. Interestingly, CB stimulation also recruited silent medullary neurons into the network and silenced active respiratory neurons. Overall, medullary population activity simply encoded the breathing pattern. In contrast, pontine population activity was tonic at baseline, but became transiently oscillatory during the acute phase, or encoded the time course of the HVR including its after-discharge.

Conclusion: Taken together, we conclude that medullary and pontine neuronal populations jointly encode the slow modulation of the respiratory motor pattern during the acute and post-hypoxic phases of the CB-evoked hypoxic ventilatory response.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.2 A Glutamate Receptor Antagonist Rescues Cardiorespiratory Chemoreflex Dysfunction Following Acute Irreversible Cholinesterase Inhibition In Female Rats

***Macedo, Breno Lopes* (1); Da Silva, Bruna Ferreira (1); Da Silva Mattar, Maurício (1); Noé, Gabriel Gavazza (1); Da Silva, Kyssilla Brisson (1); Ayub, Júlia Grigorini Mori (1); Minassa, Vítor Sampaio (2); Boina, Amanda (4); Assis, Paula Beatriz de Souza (4); Felippe, Igor Simões Assunção (3); Julian F.R. Paton (3), Sampaio, Karla Nívea (1)**

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Introduction: Standard treatment for organophosphate (OP) poisoning, consisting of atropine and pralidoxime (2-PAM), presents significant clinical limitations. The effectiveness of 2-PAM is hindered by its poor blood-brain barrier penetration and the "aging" process of the OP-AChE complex, which renders the enzyme refractory to reactivation. Previous studies from our group (Felippe et al., 2020) demonstrated that 2-PAM fails to adequately restore the respiratory and bradycardic components of the peripheral chemoreflex following chlorpyrifos (CPF) intoxication. Given that glutamate receptor overactivation contributes to OP-induced excitotoxicity, we investigated the neuroprotective potential of a glutamate receptor antagonist (Gant) as therapy.

Methods: Adult female Wistar rats (7-12 /group) received CPF (30 mg/kg, i.p.). One hour later, animals were treated with Gant (15 mg/kg, i.p.) or saline. After 24h, hemodynamic (ΔMAP and ΔHR) and ventilatory (ΔfR) delta responses to chemoreflex activation (KCN, 20 µg, i.v.) were recorded. Plasma butyrylcholinesterase (BuChE) activity was measured to confirm intoxication (Ellman's method). Data were analysed by one-way ANOVA followed by Dunnett's test (CEUA 04/2024).

Results: CPF intoxication significantly inhibited BuChE activity across all treated groups (Saline: 87.9 ± 7.09; CPF: 13.03 ± 3.47; CPF+Gant: 11.46 ± 3.60; $p<0.05$). Acute CPF exposure markedly blunted chemoreflex-induced responses. While standard therapy often fails to recover autonomic control, treatment with Gant effectively rescued the chemoreflex-evoked bradycardia (ΔHR: Saline: -70 ± 16.24; CPF: -21 ± 6.23; CPF+Gant: -97.38 ± 28.69 bpm; $p<0.05$) and the tachypneic response (ΔfR: Saline: 232 ± 17.72 vs. CPF: 169.9 ± 18.47; CPF+Gant: 220.8 ± 13.55 cpm; $p<0.05$). No significant differences were observed in ΔMAP compared to the CPF group.

Conclusion: Our findings reveal that Gant provides a robust physiological rescue of the ventilatory and chronotropic chemoreflex components in female rats. By mitigating autonomic failure where conventional oximes fall short, Gant emerges as a powerful neuroprotective adjunct to improve cardiorespiratory stability during cholinergic crises.

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2ND SYMPOSIUM - CENTRAL AND PERIPHERAL INVESTIGATION OF THE AUTONOMIC REGULATION OF CARDIOVASCULAR FUNCTION IN HEALTH, DISEASE AND INJURY

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.5 Acute Intermittent Carotid Bodies Stimulations Induce Long Term Facilitation Of Respiratory-cardiovascular Coupling, Upper Airway And Abdominal Control In Rats

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Hypertension is the leading modifiable risk factor for mortality worldwide. Neurogenic hypertension, responsible for over 50% of cases, is linked to elevated sympathetic nervous system activity. A hallmark of this condition is the exacerbation of the respiratory modulation of sympathetic nerve activity (RespSNA) and of the resulting blood pressure Traube-Hering (TH) waves, which emerges during the pre-hypertensive period and contributes to hypertension development. Carotid bodies (CBs), the peripheral chemoreceptors involved in hypoxic response, are hyperactive in hypertensive patients and animal models. Chronic intermittent CB stimulation, as observed in sleep apnea, promotes hypertension characterized by exacerbated RespSNA and TH waves. However, whether CB hyperactivity is causal in initiating these changes remains unclear. We therefore investigated whether acute intermittent CB stimulations can directly enhance RespSNA and TH waves from a physiological baseline and affect central respiratory and cardiovascular control.

We conducted our experiments using the in situ Working Heart-Brainstem Preparation in rats, a decerebrated, non-anesthetized and perfused preparation that preserves the integrity of the central cardiorespiratory control and allows simultaneous recordings of neural and physiological outputs. We performed repeated CB stimulations and mimicked acute intermittent hypoxia by injecting sodium cyanide boluses into the circulation.

Our results show that four acute and intermittent stimulations of the CB were sufficient to induce prolonged (>20 min) increases in RespSNA, TH waves, and perfusion pressure, which were prevented by carotid sinus denervation before the stimulations. These changes were accompanied by a reconfiguration of central respiratory and cardiovascular control, including an elevated respiratory heart-rate variability and an enhanced respiratory drive targeting upper airway and abdominal muscles. Notably, carotid sinus denervation performed after CB stimulation did not reverse the increase in RespSNA and TH Waves.

Our findings demonstrate that acute intermittent CB stimulations induce long-term facilitation of respiratory-cardiovascular coupling, which maintenance most likely depends on central mechanisms. This work supports the potential role of acute intermittent CB activation in hypertension development and offers insights into the transition from physiological plasticity to pathological states.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.6 Lateral Parafacial Neurons Evoked Expiratory Oscillations Driving Neurogenic Hypertension

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Abstract Hypertension is the single most important risk factor for cardiovascular diseases and remains poorly controlled. Currently, 40% of treated patients remain hypertensive. We propose that this is in part due to excessive sympathetic activity. We hypothesized that neuronal expiratory oscillations, in the medullary lateral parafacial (pFL) region, become activated in conditions of neurogenic hypertension and that silencing their activity would be antihypertensive. pFL neurons were manipulated by viral transfection. Using optogenetic and pharmacogenetic modulation, pFL neurons were either excited or inhibited in rats while recording sympathetic neurons from the rostral ventrolateral medulla (RVLM) and pontine noradrenergic A5 region, sympathetic activity, respiratory motor outflows, and arterial pressure from normotensive and hypertensive rats in vitro, in situ, and in vivo. Rats were made neurogenically hypertensive using chronic intermittent hypoxia. Optogenetic activation of pFL neurons triggered active expiration and positively modulated sympathetic activity during expiration, causing blood pressure to rise. pFL neurons projected to the RVLM and A5 presympathetic neurons and excited them during expiration, but in hypertension, only the pFL-RVLM synaptic transmission was enhanced. Pharmacogenetic inhibition of pFL neurons eliminated the expiratory-related sympatho-excitation and normalized arterial pressure in hypertensive rats. The heightened sympathetic activity inducing hypertension triggered by chronic intermittent hypoxia is caused, in the most part, by the emergence of pFL expiratory oscillations driving RVLM and A5 sympathetic vasomotor neurons and active expiration simultaneously. We propose that suppressing pFL neurons would have therapeutic potential.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.7 Investigating End-organ Regulation Through Direct Cardiac Autonomic Nerve Recordings

Dilsha Gimhani (1) - Stian Thomson (1) - Mridula Pachen (1) - Rohit Ramchandra (1) - Julia Shanks (1)

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While plasma biomarkers and heart rate variability are common surrogates for autonomic activity, they lack the temporal and spatial resolution needed to determine what the heart receives in real-time. Sympathetic transduction is the study of how impulses from the sympathetic nervous system affect end-organ function. While this relationship is well-established for resting muscle sympathetic nerve activity (MSNA), direct cardiac sympathetic transduction remains poorly understood, and the parallel vagal transduction of cardiac end-organ responses has not yet been assessed. We aimed to investigate how directly recorded resting cardiac sympathetic nerve activity (CSNA) and cardiac vagal nerve activity (CVNA) dynamically regulate cardiac function. Adult sheep were instrumented to achieve direct, intra-thoracic, recordings of CSNA or CVNA, depending on group. Simultaneous measurements of beat-to beat, heart rate, coronary blood flow, coronary vascular conductance, cardiac output, and mean arterial pressure were acquired. All experiments were performed at least one week after instrumentation surgery in conscious animals at rest. Modified signal-transduction methods were applied to measure how spontaneous bursts of neural activity trigger immediate end-organ responses. Signal transduction analysis revealed that each spontaneous CSNA burst triggered a significant elevation in heart rate, immediately followed by a compensatory increase in coronary blood flow. Crucially, these tachycardic changes were graded according to the precise size and pattern of the preceding CSNA bursts, and were significantly attenuated following propranolol. CVNA exhibits distinct burst profiles; spontaneous CVNA bursts triggered rapid, transient decreases in heart rate that was dependent on the specific burst type, with burst incidence correlating with blood pressure. Establishing end-organ effects from directly recorded cardiac autonomic nerve activity will help establish a high-resolution framework for understanding autonomic control of the heart in conscious large mammals.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.8 Heart And Respiratory Central Regulation Changes During The Acute Phase Of Brain Injury.

Baptiste Balanca (1)

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The autonomic regulation of cardiovascular function depends on dynamic interactions between central neural networks and peripheral physiological outputs. In patients with acute brain injury, these interactions may be profoundly altered during the early phase after injury. Respiratory-related heart rate variability (RespHRV) may provide a clinically accessible marker of this central cardiorespiratory dysregulation. In this workshop I will discuss the impact of acute brain injury and neurocritical care on respiratory and cardiovascular functions with a focus on RespHRV and the specific contribution of cortical spreading depolarization (SD) which are landmark events that characterize brain injury progression.

The presentation will rely on high-resolution multimodal neuromonitoring performed in intensive care patients with acute brain injury. Continuous neurophysiological (e.g., intracranial pressure, electrocorticography) and cardiorespiratory signals allow the temporal analysis of cerebral insults and their relationship with RespHRV.

Brain-injured neuro-ICU patients had a much lower respiratory heart rate variability (RespHRV) amplitude than healthy controls (median 1.04 [0.45–1.96] vs. 6.21 [4.08–9.34] bpm; $p < 0.001$). Their RespHRV phase was inverted, with peak heart rate occurring during expiration instead of inspiration. Within patients, machine-triggered (fully controlled) ventilation and higher levels of sedation were associated with further reductions in RespHRV amplitude. While SD were associated with a mild respiratory rate variability increase, they did not change RespHRV. In addition, high levels of sedation and opioid administration were associated with a reduction in Resp HRV amplitude and heart rate variability.

Together, these findings indicate markedly impaired central brainstem generation of RespHRV in acute brain injury, with ventilation mode and sedation exerting additional influence.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.3 Spontaneous Bursts Of Muscle Sympathetic Nerve Activity Transiently Reduce Skeletal Muscle Vascular Compliance In Humans

Nathaniel Iannarelli (1)* - *Kyle Brown (1)* - *Tanikan Hartley (1)* - *Felicia Bouaban (1)* - *Cameron Lynn (1)* - *Julia Spafford (1)* - *Stephen Cheung (1)* - *Deborah O'leary (1)* - *Stephen Klassen (1)

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Introduction: Previous data demonstrate that skeletal muscle vascular compliance is reduced in response to sympathetic adrenergic stimulation. However, whether spontaneous bursts of muscle sympathetic nerve activity (MSNA) affect beat-by-beat changes in vascular compliance remains uncertain. This study tested the hypothesis that spontaneous bursts of MSNA elicit transient reductions in skeletal muscle vascular compliance that are graded to MSNA burst amplitude.

Methods: Blood pressure (finger photoplethysmography), superficial femoral artery blood flow velocity (Doppler Ultrasound), and MSNA (peroneal microneurography) were recorded during 5-min of baseline rest in eight healthy males (25 ± 3 years). A lumped Windkessel model was used to calculate indices of leg vascular conductance and leg vascular compliance. Signal averaging quantified percent changes in mean arterial pressure, leg vascular conductance, and leg vascular compliance following MSNA bursts, non-bursts, and a white noise control. Mixed-effects modeling with post-hoc t-tests and repeated measures correlations were performed.

Results: Following MSNA bursts, mean arterial pressure increased and leg vascular conductance decreased (both $p < 0.001$ vs. white noise control). Peak mean arterial pressure (+2.7 ± 1.0 %ΔmmHg) and nadir conductance (-4.5 ± 2.4 %ΔmL/min/mmHg) responses occurred during cardiac cycle 7 following MSNA bursts. Following non-bursting cardiac cycles, mean arterial pressure decreased and leg vascular conductance increased (both $p < 0.001$ vs. white noise control). Nadir mean arterial pressure (-1.2 ± 0.4 %ΔmmHg) and peak conductance (+3.6 ± 2.5 %ΔmL/min/mmHg) responses occurred during cardiac cycle 7 following non-bursting sequences. Following MSNA bursts, leg vascular compliance decreased ($p < 0.001$ vs. white noise control) and reached a nadir during cardiac cycle 6 (-3.9 ± 2.4 %Δcm/s/mmHg). Following non-bursting cardiac cycles, leg vascular compliance increased ($p = 0.014$ vs. white noise control) and reached a peak during cardiac cycle 7 (+3.0 ± 1.8 %Δcm/s/mmHg). Repeated measures correlations revealed that larger amplitude MSNA bursts produced larger reductions in leg vascular compliance (rrm= -0.50, $p = 0.042$).

Conclusions: Spontaneous bursts of MSNA elicit transient reductions in skeletal muscle vascular compliance that are graded to MSNA burst amplitude. These data provide evidence that the sympathetic nervous system exerts moment-to-moment control over skeletal muscle vascular compliance in humans.

TOPIC 07 - Molecular and systems-level mapping of autonomic circuits and brain–body integration

O.4 A Glutamatergic Interneuron Circuit In The Lateral Parafacial Region Controlling Active Expiration And Arterial Pressure In Mice

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The lateral parafacial (pFL) region, involved in generating active expiration, has recently been recognized as an integrative hub linking respiratory and cardiovascular outputs. This region contains excitatory neurons and interneurons; however, the specific contribution of glutamatergic pFL interneurons in modulating breathing and cardiorespiratory outflow remains unclear. We used Vglut2(cre/cre) mice injected with adeno-associated viruses to express excitatory hM3D-Gq receptors in pFL glutamatergic interneurons and assessed the effects of chemogenetic activation on pulmonary ventilation in non-anesthetized mice (n=10). In another group of mice, we expressed channelrhodopsin in pFL glutamatergic interneurons and evaluated the effects of its photostimulation on cardiorespiratory outflow in in situ preparations (n=11). Ethical committee #1143/2022. Paired and unpaired Student's t-tests were used. The phenotype of transfected interneurons was confirmed using mice expressing GFP in Vglut2-positive neurons, which demonstrated that 98% of transfected pFL interneurons were glutamatergic (n=4). At rest, chemogenetic activation of pFL glutamatergic interneurons reduced respiratory frequency (149.2±53.19 vs 213.9±60.56 cpm; p=0.002) and increased tidal volume (10.2±3.36 vs 7.91±1.31 mL.Kg-1; p=0.02), without affecting pulmonary ventilation (1620±1044 vs 1732±738.3 mL.Kg-1.min-1). Respiratory cycle duration also increased (380.1±124.5 vs 287.6±64.37 ms; p=0.01) due to an enhancement in expiration (287.8±138 vs 159.9±40.27 ms; p=0.01). The area of early (4.17±1.12 vs 2.87±0.52, p=0.006) and late expiratory flow (3.06±1.05 vs 0.69±0.23, p=0.0001) increased, indicating active expiration recruitment. Photostimulation (5s–20Hz) of pFL glutamatergic interneurons in situ increased expiratory abdominal (293.6±137 vs 100±0 %, p<0.0001) and hypoglossal activity (388.5±248 vs 100±0 %, p<0.0001), as well as perfusion pressure (58±7 vs 56±7 mmHg; p=0.001), while inhibited the phrenic inspiratory activity (0±0 vs 0.8±0.32 Hz, p<0.0001). Brief (10 ms) stimulation during inspiration reduced the phrenic inspiratory activity (-0.03±0.07 vs -0.77±0.06 Δ%, p<0.0001) and cycle duration (-0.1±0.04 vs -0.62±0.19 Δ%, p<0.0001). Stimuli during early expiration shortened cycle duration (-0.01±0.08 vs -0.4±0.24 Δ%, p=0.01), while at late expiration prolongated it (0.54±0.35 vs -0.03±0.08 Δ%, p<0.0001). These findings identify pFL glutamatergic interneurons as a functional brainstem circuit modulating pulmonary ventilation by controlling expiratory motor output. Additionally, these interneurons may contribute to cardiovascular regulation, supporting an integrative cardiorespiratory role of pFL region.

3RD SYMPOSIUM 3 - BEYOND THE AVERAGE HUMAN: NEW INSIGHTS FROM INTERINDIVIDUAL VARIABILITY IN AUTONOMIC CONTROL

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.9 Interindividual Variability In Muscle Sympathetic Nerve Activity At Rest And During Stress

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For more than five decades, microneurographic recordings of muscle sympathetic nerve activity (MSNA) have provided a unique window into sympathetic neural control at rest and during stress. A hallmark of MSNA recordings is the substantial interindividual variability, despite excellent test-retest reliability. Even among healthy adults MSNA can exhibit several-fold differences and is influenced by biological sex, body composition, and aerobic fitness. Appreciating the interindividual variability in MSNA is important for interpreting differences between healthy and clinical populations, particularly in studies with small sample sizes, and raises the important question 'what is normal MSNA?'. The physiological significance of interindividual variability in resting MSNA remains incompletely understood. Despite large differences in sympathetic outflow, healthy adults demonstrate little or no relationship between resting MSNA and blood pressure. Whether variability in resting MSNA reflects differential sympathetic outflow to target organs, differences in sympathetic vascular transduction, or compensation for underlying differences in vascular properties remains unclear. In contrast, a positive association between resting MSNA and blood pressure has been observed in hypertensives, implicating neurogenic mechanisms in the development and maintenance of elevated blood pressure. Interindividual variability is also evident in MSNA responses to acute stressors, such as exercise and mental stress, where sympathetic and blood pressure responses can be dissociated. The integrated mechanisms contributing to this interindividual variability will be discussed, including the potential roles of arterial baroreflex loading and absolute contraction intensity during exercise. Finally, the talk will argue that interindividual differences in MSNA should not be viewed simply as experimental noise, but rather as a biologically meaningful characteristic that provides unique insight into the mechanisms governing sympathetic regulation at rest and during stress.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.10 Interindividual Variability In Sympathetic Contributions To Hypertension And Response To Interventional Therapies

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Hypertension is not a single disease but a syndrome with multiple underlying mechanisms, including variable sympathetic nervous system contributions to blood pressure. Direct recordings of muscle sympathetic nerve activity showed marked interindividual variability in sympathetic traffic among patients with hypertension, indicating that elevated blood pressure is not uniformly driven by sympathetic overactivity. This concept is reinforced by studies showing highly variable blood pressure responses to pharmacological sympathetic inhibition. While some patients exhibit substantial reductions in blood pressure, others show little response, suggesting that not all forms of hypertension are “sympathetic”. Moreover, the mechanisms driving sympathetic activity may differ between individuals with hypertension with varying contributions of baroreflex dysfunction, peripheral chemoreflex sensitization, and central neural pathways. The implications for therapeutic strategies targeting the sympathetic nervous system are obvious, particularly for invasive strategies like baroreflex activation therapy or renal denervation. Variable blood pressure responses to interventions targeting the sympathetic nervous system raise important questions regarding patient selection, underlying mechanisms, and predictors of therapeutic success. A better understanding of individual differences in sympathetic cardiovascular regulation may help guide the development and application of more precise approaches to hypertension management.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.11 Interindividual Variability In Autonomic And Haemodynamic Responses In Pulmonary Arterial Hypertension

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Introduction. Autonomic dysfunction is increasingly identified as a driver of disease and exertional intolerance in pulmonary arterial hypertension (PAH) and may offer novel targets to improve wellbeing in PAH. We hypothesised that three mechanisms, namely the skeletal muscle metaboreflex, peripheral chemoreflex and pulmonary arterial baroreflex are pathophysiologic drivers in PAH.

Methods. Firstly, to assess the effect of the skeletal muscle metaboreflex on ventilation and the pulmonary vasculature, isometric handgrip exercise with post-exercise circulatory occlusion was performed in 14 PAH patients and 14 healthy controls, with measurement of ventilatory (spirometer) and pulmonary vascular (transthoracic echocardiography) responses. Secondly, to assess the effect of the peripheral chemoreflex on exercise ventilatory efficiency and exercise duration, we measured peripheral chemoreflex sensitivity (PChS) using a progressive hypoxic rebreathe. Then in a blinded randomised cross-over design, 9 PAH patients undertook submaximal constant work-rate cycle exercise testing under normal saline (control) and low-dose dopamine (2 µ·kg-1·min-1) intravenous infusion conditions. Finally, to assess the contribution of pulmonary arterial baroreceptors to muscle sympathetic nerve activity (MSNA), 7 PAH and 2 chronic thromboembolic pulmonary hypertension patients inhaled nebulised iloprost to lower pulmonary artery pressure, with measurement of MSNA (microneurography) and pulmonary vascular responses (transthoracic echocardiography).

Results. The muscle metaboreflex ventilatory response was exaggerated in PAH compared to healthy controls (1.7±1.4 vs. -0.4±1.4 L·min-1; p<0.001), albeit with inter-individual variability. Borg dyspnoea score during hand-grip exercise in PAH patients was correlated with the metaboreflex ventilatory response (r=0.581, p=0.029). In individuals with elevated baseline PChS (n=4; above median), V̇E/V̇CO2 was reduced (p=0.001) and exercise duration increased (saline 435±365 vs. dopamine 680±482 s; p=0.025) with dopamine, whereas no differences were observed in patients with lower PChS. Iloprost nebulisation produced variable magnitudes of pulmonary vascular responses. The change in MSNA burst amplitude and total activity was inversely correlated with the increase in pulmonary arterial acceleration time (R2=0.632, p=0.018 and R2=0.493, p=0.052 respectively).

Conclusions. There are significant inter-individual differences in autonomic reflex function in PAH which importantly appear to influence end-responses. These results suggest targeting autonomic dysfunction in PAH requires understanding the drivers of such variability and identifying the autonomic phenotype of individuals.

TOPIC 01. Autonomic Dysfunction In Neurodegenerative And Orthostatic Disorders

S.12 Beyond The Heart Rate Threshold: Clinical Variability In Orthostatic Disorders

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Abstract Current diagnostic criteria for postural orthostatic tachycardia syndrome (POTS) rely primarily on an orthostatic heart rate threshold, yet this physiological definition may not adequately reflect the clinical experience of patients. Emerging data from large observational cohorts suggest that individuals who narrowly miss diagnostic criteria can experience symptom burden, impaired quality of life and healthcare utilisation comparable to those who meet formal diagnostic thresholds. This presentation will examine interindividual variability in orthostatic intolerance using data from the Australian POTS Registry and related cohort studies, exploring the relationship between physiological responses, autonomic symptom burden and patient-reported outcomes. The presentation will consider whether orthostatic disorders exist along a clinical continuum and discuss the implications for diagnosis, patient selection, research design and management. Recognising variability beyond traditional diagnostic cut-points may provide a more clinically meaningful framework for understanding orthostatic disorders and guiding future research.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.5 Who Benefits From Slow Breathing? Mindfulness, Anxiety, And Worry Contribute To Heterogeneity In Blood Pressure Responses

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Slow breathing has been investigated as a non-pharmacological approach to reduce norepinephrine and vascular resistance based on respiratory-sympathetic coupling mechanisms (i.e., individuals with higher resting breathing rates exhibit greater muscle sympathetic nerve activity and vascular resistance). However, there are mixed results on the effectiveness of slow breathing in reducing blood pressure. We tested the hypothesis that high inter-individual variability masks effectiveness of slow breathing in mean datasets and that blood pressure responses to self-paced slow breathing are associated with psychological traits.

Healthy young men (n=13) performed baseline breathing followed by 15 min of self-paced slow breathing in the supine position (13.6±1.2 breaths/min vs 7.9±6.4 breaths/min, $p<0.05$). Blood pressure, heart rate, and breathing rate were continuously recorded, and forearm blood flow was measured at discrete time points. Participants completed validated assessments of mindfulness, trait anxiety, and worry.

Mean arterial pressure (MAP) responses to slow breathing were modest when pooled across all subjects (-1.7±0.8 mmHg vs baseline, $p>0.05$). Notably, individual responses were highly variable, with both decreases or increases in MAP observed during the slow breathing period (range: -5.5 mm/Hg to +1.1 mmHg). Delta MAP with slow breathing was correlated with individual scores on psychological surveys, including mindfulness ($r=0.36$), trait anxiety ($r=0.39$), and worry ($r=0.37$).

These findings demonstrate that blood pressure responses to slow breathing show wide intra-individual differences that are related to psychological characteristics. Consideration of psychological traits may improve effectiveness of slow breathing interventions by informing individualized approaches to non-pharmacological blood pressure regulation techniques. For individuals with high mindfulness, low worry, and low anxiety, slow breathing can be a very effective method to acutely reduce blood pressure.

TOPIC 10: Development, aging and sex differences in autonomic function

O.6 Cardiac Autonomic Response To Active Standing And Olfactory Function In Older Adults

***Sae Uchida (1)* - Daichi Morihara (2) - Fusako Kagitani (1) - Hiroyuki Suzuki (3)**

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Introduction: Cardiovascular dysfunction has been proposed as a potential risk factor for olfactory impairment in older adults; however, the underlying association remains insufficiently clarified. This study investigated whether older adults who demonstrate reduced cardiac autonomic responsiveness during orthostatic stress also exhibit poorer olfactory discrimination ability.

Methods: A total of 100 community-dwelling older adults aged 60 years and above, all of whom were living independently, participated in this study. Cardiac autonomic function, which contributes to the baroreflex-mediated cardiovascular response, was assessed by measuring the increase in heart rate during the postural transition from sitting to standing, expressed as the maximum change in heart rate (ΔHRmax). Participants were subsequently classified into small and large response groups according to the mean ΔHRmax value. Time domain analysis of heart rate variability was also performed during seated rest. Specifically, the root mean square of successive heartbeat interval differences (RMSSD) was evaluated as an index of cardiac vagal modulation. Olfactory function was assessed using a discrimination task that tested participants' ability to distinguish between similar-smelling odorants. Olfactory performance was then compared between participants with lower and higher cardiac autonomic responsiveness, defined by smaller and larger ΔHRmax values, respectively. This comparison was conducted separately in the young-old group, defined as participants younger than 75 years, and the old-old group, defined as participants aged 75 years and above.

Results: The mean ΔHRmax was 8.1 ± 3.5 (mean ± SD) beats per minute. A significantly greater proportion of participants in the smaller-ΔHRmax group than in the larger-ΔHRmax group were unable to discriminate between the odorants. This pattern was observed in both age categories but was more pronounced among the older participants, particularly those in the old-old group. Within the old-old group, the participants with smaller ΔHRmax demonstrated lower heart rate variability than those with larger ΔHRmax.

Conclusion: These findings suggest that a blunted heart rate response to active standing, potentially reflecting reduced cardiac vagal modulation and impaired autonomic adaptability to orthostatic stress, is associated with poorer olfactory discrimination ability. This association appears to be particularly evident among adults aged 75 years and older.

4TH Symposium - EARLY DETECTION AND MONITORING OF DISEASE PROGRESSION IN PROTEIN MISFOLDING DISEASES AND LYSOSOMAL STORAGE DISORDER

TOPIC 06: Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.13 Screening Of Patients With Polyneuropathy And Neurogenic Autonomic Dysfunction For Early Detection Of Amyloidosis And Lewy Body Disease

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Protein misfolding disorders such as AL amyloidosis, hereditary transthyretin amyloidosis (ATTRv), and synucleinopathies are characterized by pathological protein aggregates, including amyloid fibrils and α-synuclein. These deposits can lead to multisystem disease with organ dysfunction, polyneuropathy, and neurogenic autonomic dysfunction.

The diagnostic approach to polyneuropathy will be reviewed focusing on length-dependent and generalized small-fiber polyneuropathy using the Utah Early Neuropathy Scale and the modified Kumamoto score. The modified Kumamoto score provides standardized phenotyping of neurological, autonomic, and visceral involvement. Cardiac [123I]Metaiodobenzylguanidine (MIBG) scintigraphy and 99mTc-DPD scintigraphy enables detection of cardiac sympathetic denervation and transthyretin amyloid deposition, respectively before clinically significant organ dysfunction develops.

Results from screening 100 patients with polyneuropathy and neurogenic autonomic dysfunction for ATTRv are presented. Only one patient was diagnosed with ATTRv, illustrating its rarity among this patient population in Denmark. However, active disease in minimally symptomatic ATTRv mutation carriers can be detected despite the absence of large-fiber neuropathy and clinically overt cardiomyopathy through small-fiber neuropathy with anhidrosis, reduced intraepidermal nerve fiber density, abnormal DPD scintigraphy, and amyloid deposition in abdominal fat aspirate and myocardial biopsy. Early diagnosis allows timely initiation of disease-modifying therapy.

Autonomic dysfunction can represent an early manifestation of body-first Lewy body disease, preceding motor and cognitive symptoms by decades with orthostatic hypotension, constipation, bladder dysfunction, and REM sleep behaviour disorder. Case illustration of the value of autonomic phenotyping and cardiac MIBG scintigraphy for identifying prodromal Lewy body disease.

Avenue media
Conference & Expo

TOPIC 06: Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.14 Polyneuropathy As An Early Manifestation Of Lewy Body Disease?

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Lewy body diseases (LBD) are progressive neurodegenerative disorders characterized by pathological aggregation of α -synuclein in the central and peripheral nervous system. The clinical spectrum ranges from early manifestations such as pure autonomic failure and REM sleep behaviour disorder (RBD) to Parkinson's disease and dementia with Lewy bodies(1). Although polyneuropathy has been reported to be more common in Parkinson's disease than in the general population(2), it remains unknown whether idiopathic polyneuropathy may represent an early manifestation of LBD. Following a clinical observation(3), we conducted a pilot study of patients with idiopathic polyneuropathy and autonomic dysfunction (n=19) to address this question. Subsequently, we established a prospective cohort, with enrollment for the baseline assessment now nearing completion (target n=81). Participants will undergo follow-up at 2.5 and 5 years.

Our research uses a comprehensive multimodal approach, including autonomic reflex testing, cardiac 123I-MIBG scintigraphy, skin biopsy for α-synuclein seed amplification assay (SAA), video-polysomnography, olfactory testing, dopamine transporter imaging (18F-FE-PE2I-PET/CT), and cognitive and motor assessments.

Results from the pilot study will be presented. Pathological cutaneous α-synuclein and cardiac sympathetic denervation ("invisible heart") were observed in a subset of participants with idiopathic polyneuropathy. These findings raise the possibility that idiopathic polyneuropathy may represent an early manifestation of LBD in a subset of patients. Longitudinal follow-up will determine whether these findings are associated with an increased risk of developing clinically manifest LBD.

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TOPIC 06: Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.15 Monitoring Of Patients And Asymptomatic Carriers With Hereditary Transthyretin Amyloidosis To Identify Disease Progression

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Introduction: The availability of disease-modifying therapies has transformed the management of hereditary transthyretin amyloidosis (ATTRv), making early diagnosis and timely treatment initiation critical determinants of outcome. However, no universally accepted strategy exists for monitoring symptomatic patients, and identifying the transition from asymptomatic carrier status to clinically manifest disease remains challenging. Emerging evidence suggests that autonomic dysfunction may represent one of the earliest detectable manifestations of ATTRv.

Methods: We reviewed current literature and expert recommendations on ATTRv monitoring and integrated them with the experience of the Emilia-Romagna ATTR Working Group, a multidisciplinary regional network comprising 19 neurologists and 25 cardiologists currently following approximately 120 patients with ATTRv amyloidosis. Neurological, autonomic, neurophysiological, and cardiological assessments were evaluated to identify practical and sustainable approaches for longitudinal monitoring and early detection of disease progression.

Results: ATTRv progression is characterized by heterogeneous multisystem involvement affecting peripheral nerves, the autonomic nervous system, and the heart. No single biomarker adequately captures disease progression across all phenotypes. Current evidence supports a multimodal monitoring strategy including neurological examination, disability scales, autonomic questionnaires, neurophysiological studies, cardiovascular autonomic testing, cardiac biomarkers, imaging studies, and patient-reported outcome measures. In asymptomatic carriers, surveillance initiated before the predicted age of disease onset may facilitate the detection of subclinical neurological, autonomic, and cardiac involvement. Based on these principles, the Emilia-Romagna ATTR Working Group developed a standardized regional monitoring pathway aimed at harmonizing evaluations and ensuring equitable access to diagnostic and therapeutic opportunities. Within this framework, cardiovascular autonomic testing emerged as a promising tool for detecting early disease-related abnormalities. Preliminary observations suggest that asymptomatic carriers may exhibit subtle impairments of cardiovascular autonomic control, particularly during the Valsalva manoeuvre, despite the absence of overt neuropathy or autonomic symptoms.

Conclusion: ATTRv requires a multidisciplinary and standardized monitoring strategy. Systematic assessment of symptomatic patients is essential to evaluate disease progression and therapeutic response, while surveillance of asymptomatic carriers may facilitate the detection of phenoconversion. Cardiovascular autonomic testing may provide sensitive biomarkers of early disease expression and help identify carriers at risk of developing overt disease. Regional collaborative networks represent an effective model for implementing harmonized and sustainable monitoring pathways in ATTRv amyloidosis.

TOPIC 08: Autonomic Control Of Metabolism And Energy Homeostasis

S.16 Similarities And Differences Between Fabry Disease And TTR Amyloidosis

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Fabry disease (FD) and transthyretin amyloidosis (ATTR) are rare, progressive, multi-system diseases with variable clinical manifestations and some overlap of clinical phenotypes, such as left ventricular hypertrophy, heart failure, cardiac arrhythmia, renal failure, carpal tunnel syndrome, small fiber neuropathy with subtle or prominent autonomic dysfunction including, e.g. sudomotor and gastrointestinal dysfunction. Moreover, there is a wide variety of clinical presentations of early or late onset, male or female FD with its more than 1000 mutations in the X-chromosomal gene encoding the α-galactosidase A enzyme and thus causing α-galactosidase A deficiencies with subsequent intracellular, lysosomal glycosphingolipid storage damaging many organs, including kidneys, heart, brain, peripheral and autonomic nervous system.

In ATTR, a variability of clinical manifestation might also complicate diagnosis as there are 130 to 150 mutations of the autosomal dominant TTR gene encoding Transthyretin, a tetramer Transporting Thyroxine and Retinol, (accounting for the abbreviation TTR). The mutations trigger a variable instability of the TTR-tetramers which results in unstable TTR-monomers that misfold into still soluble oligomers but then aggregate to insoluble amyloid fibrils, and ultimately cause extracellular amyloid deposits in various organs, particularly the heart and small and large fiber nerves.

Thus, differentiating both orphan diseases may be difficult, particularly in older patients and in a clinical outpatient setting. However, a misdiagnosis or delayed diagnosis of either disease may cause progressive, ultimately irreversible neurological, cardiac, or renal complications. In contrast, the early diagnosis and treatment with disease modifying therapies may prevent or slow disease progression.

FD can be treated with intravenous enzyme replacement therapy, oral chaperone therapy, or an emerging substrate reduction therapy. ATTR can be improved with TTR-stabilizers, Antisense Oligonucleotides or small interfering RNA both silencing the TTR mRNA in the liver and thus limiting or stopping TTR-protein production and thus amyloid formation.

Ultimately genetic testing not only differentiates the two diseases but may also guide adequate treatment. However, there are also clinically distinct differences in the presentation of organ dysfunction such as typical cardiologic, renal, autonomic, cerebrovascular and other neurological manifestations that facilitate the correct clinical differentiation of both diseases. These differences that shall be further discussed.

TOPIC 06: Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.7 Cardiovascular Autonomic Failure In Hereditary Non-transthyretin Amyloidosis

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Introduction: Autonomic dysfunction is a common feature in hereditary transthyretin amyloidosis (ATTRv), but has not been systematically described in other genetic types of amyloidosis such as gelsolin (AGel), apolipoprotein A1 (AApoA1), and fibrinogen Aα-chain amyloidosis (AFib). This study aimed to quantitatively investigate cardiovascular autonomic failure in these rare diseases, and to compare cardiovascular autonomic dysfunction to patients with ATTRv.

Methods: This retrospective study enrolled patients with genetically confirmed diagnosis of AGel, AApoA1, and AFib. Age- and sex-matched control patients with ATTRv were included. All participants underwent standardised cardiovascular autonomic function testing (AFT), a subgroup had ambulatory 24h blood pressure monitoring (ABPM) with autonomic patient diary. Stages of autonomic failure were defined according to AFT results: stage 0 (normal AFT), stage I (mild parasympathetic and/or sympathetic impairment), and stage II (presence of neurogenic orthostatic hypotension (nOH)).

Results: A total of 12 patients were included. Overall, 9/11 (82%) patients had abnormal AFT. 8/11(73%) presented with autonomic failure stage I, and only 1/11 (9%) patient with AApoA1 had nOH. In the matched ATTRv cohort, 4/12 (33%) presented with nOH. There were no significant differences in cardiovascular autonomic parameters when comparing ATTRv versus non-ATTRv patients. ABPM was available in two patients: one individual with AFib (stage I) had normal circadian BP rhythm, while one patient with AApoA1 (stage II) was a reverse dipper.

Conclusion: Cardiovascular autonomic dysfunction is very prevalent in genetic non-TTR amyloidosis, but is usually mild. Quantitative AFT could help to monitor disease progression. Prospective studies are needed to investigate dysfunction of other autonomic domains in these patients.

TOPIC 06: Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.8 Real-world Impact Of vutrisiran on Autonomic Dysfunction And Disability In Hereditary Transthyretin Amyloidosis

Micol Gianoli (1)* - *Carla Fasano (1)* - *Simone Longhi (2)* - *Irene Ruotolo (3)* - *Roberto D'angelo (1)* - *Rita Rinaldi (1)* - *Federica Provini (1)* - *Giovanna Calandra Buonaura (1)* - *Pietro Guaraldi (1)

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Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a multisystem disorder caused by the deposition of misfolded transthyretin (TTR), commonly affecting peripheral nerves and the heart. Amyloid deposition often involves autonomic nerves early in the disease course, resulting in progressive autonomic dysfunction that substantially contributes to morbidity and reduced quality of life. Vutrisiran (Amvuttra), an RNA interference therapeutic targeting hepatic TTR production, is approved for the treatment of ATTRv amyloidosis and has demonstrated benefits on neurological and cardiac manifestations. However, autonomic outcomes were not specifically assessed in the pivotal registration trials, leaving the effect of vutrisiran on dysautonomia largely unexplored.

Methods: We retrospectively evaluated 57 consecutive patients with ATTRv amyloidosis treated with vutrisiran at our centre. Demographic and clinical data were collected from 9 months before treatment initiation through 18 months of follow-up. Autonomic symptom burden was assessed using the Composite Autonomic Symptom Score-31 (COMPASS-31), while disability and quality of life were evaluated using the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire. Longitudinal changes in autonomic symptoms and disability were analyzed using repeated-measures approaches.

Results: COMPASS-31 domain scores remained overall stable throughout follow-up, suggesting preservation of autonomic function after treatment initiation. The gastrointestinal domain showed a directional trend toward improvement over time. Norfolk QOL-DN scores demonstrated a descriptive reduction from baseline to 18 months, indicating a potential improvement in disease-related disability. Baseline COMPASS-31 domain scores were not independently associated with Norfolk QOL-DN at 9 months after adjustment for baseline disability. However, orthostatic intolerance exhibited a positive directional trend, suggesting that a greater autonomic symptom burden at baseline may contribute to worse functional outcomes.

Conclusion: These real-world findings suggest that treatment with vutrisiran is associated with longitudinal stability of autonomic symptoms in patients with ATTRv amyloidosis. Moreover, the relationship between autonomic symptom burden and disability underscores the clinical relevance of dysautonomia and supports the incorporation of comprehensive autonomic assessment into routine disease management.

5TH Symposium - CARDIOVASCULAR AUTONOMIC DISORDERS IN CLINICAL PRACTICE

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.17 Mechanistic Insights Into POTS And Ist: Autonomic Dysfunction, Inflammation And Hemodynamic Regulation

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The incidence of autonomic disorders steeply increased following COVID-19 pandemic, in particular of postural orthostatic tachycardia syndrom (POTS) and inappropriate sinus tachycardia (IST). Although separate diagnostic definitions have been established, the clinical delineation between the two disorders remains imprecise. We investigated 270 patients divided into a POTS group, an IST group and a dual pathology group (POTS+IST). The cohort included 147 POTS patients, 41 IST patients, and 82 dual pathology patients. Hypertension was more prevalent in patients with IST (37%) compared to POTS (10%) and dual pathology (21%; p<0.001). Presyncope/syncope was most frequently reported by dual pathology patients (POTS 59%; IST 46%; dual pathology 70%; p=0.04). Nausea was reported more often in POTS (63%) than in IST (37%; p=0.004). All groups reported a similar symptom burden according to the mean total Malmö POTS Symptom Score (MAPS; POTS 61 points, IST 61 points, dual pathology 66 points). Palpitations were the most frequently reported symptom (POTS 91%; IST 85%; dual pathology 94%).

Resting systolic blood pressure was slightly higher in IST (124±18 mmHg) compared to POTS (117±14 mmHg; p=0.001) but was comparable to dual pathology (124±12 mmHg). Functional exercise capacity, as assessed by the six-minute walk test, was reduced across all groups, with no significant differences observed (POTS 430±162 m; IST 461±162 m; dual pathology 421±130 m; p=0.221; normal range 580-610 m). Left ventricular ejection fraction was preserved and comparable across all subgroups.Ivabradine was the most frequently prescribed pharmacological agent, followed by beta-blockers, with comparable use across all groups. The use of Pyridostigmine (POTS 42%; IST 12%; dual pathology 34%; p=0.003), Fludrocortisone (POTS 11%; IST 0%; dual pathology 4%; p=0.02) and Midodrine (POTS 24%; IST 7%; dual pathology 13%; p=0.02) were all more frequently prescribed in the POTS group.

In conclusion, POTS (54%) and dual pathology (30%) were more common than isolated IST (15%). We have observed that IST exhibits clinical and hemodynamic profiles with higher rates of hypertension and higher resting SBP, whereas POTS and dual pathology exhibit higher rates of presyncope, cognitive impairment, and nausea.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.18 Stroke Volume & Cerebral Blood Flow: Role of CO2 and Heart Rate - Implications for POTS

Jaquine Baker (1), presented by ***Rashnim Hira (1)***

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Postural orthostatic tachycardia syndrome (POTS) is characterized by excessive orthostatic tachycardia and chronic symptoms including light-headedness, palpitations, breathlessness, brain fog, and presyncope. Postural hyperventilation is common in POTS, but the mechanisms linking respiratory changes, hemodynamic instability, and cerebral perfusion remain incompletely understood. We present data from two complementary studies examining the roles of carotid body activity, stroke volume, heart rate, and cerebral blood flow in POTS. In a randomized hyperoxia study comparing patients with POTS to individuals without POTS, exaggerated carotid body activity did not appear to explain postural hyperventilation. Instead, reductions in stroke volume and cerebral perfusion emerged as potential drivers of ventilatory and sympathetic responses. Therefore, to determine the role of tachycardia in cerebral perfusion, we next used a controlled atrial pacing model to isolate the hemodynamic effects of increasing heart rate. Excessive tachycardia impaired cerebral perfusion through reductions in stroke volume, even when mean cerebral blood flow appeared relatively preserved. Together, these findings suggest that tachycardia-mediated reductions in stroke volume and cerebral perfusion may contribute to brain fog, presyncope, and symptom burden in POTS.

TOPIC 06. Autonomic Dysfunction In Neurodegenerative And Orthostatic Disorders

S.19 Cardiovascular Autonomic Abnormalities In Post-acute Sequelae Of COVID-19: Mechanistic Overlap With POTS And Implications For Management

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Abstract Post-acute sequelae of COVID-19 (PASC) are frequently associated with persistent cardiovascular symptoms, with increasing evidence that autonomic nervous system dysfunction contributes to their pathophysiology. This presentation will examine cardiovascular autonomic abnormalities in PASC using objective autonomic, haemodynamic and biomarker data, highlighting the high prevalence of postural orthostatic tachycardia syndrome (POTS) within affected individuals. It will explore mechanistic overlap between PASC and POTS, including abnormalities in autonomic regulation, cerebral perfusion and inflammatory pathways, and discuss the implications for diagnosis, patient phenotyping and targeted management.

TOPIC 06. Autonomic Dysfunction In Neurodegenerative And Orthostatic Disorders

S.20 Clinical presentation & diagnostic work-up of post-viral/autoimmune POTS

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Background: Orthostatic intolerance may develop following viral infection and, less commonly, vaccination, with postural orthostatic tachycardia syndrome (POTS) representing one of the most frequently diagnosed cardiovascular autonomic disorders (CAD) in affected individuals.

Methods: This symposium presentation outlines the diagnostic work-up for suspected post-viral and post-vaccination cardiovascular autonomic disturbances and summarizes the clinical presentation of POTS in post-viral and autoimmune conditions, with a particular focus on the COVID-19 pandemic. The content is based on early experiences gathered from European Autonomic Centers participating in the EAN-EFAS survey on the impact of the COVID-19 pandemic on clinical autonomic practice, evidence from PubMed-indexed cohort studies and systematic reviews, and findings from a tertiary single-center cohort of individuals evaluated for suspected cardiovascular autonomic disturbances following SARS-CoV-2 infection or COVID-19 vaccination. Demographic characteristics, clinical (autonomic) features, results of autonomic function testing, and the frequency of final diagnoses were analyzed.

Results: The COVID-19 pandemic led to a marked increase in referrals for suspected cardiovascular autonomic disturbances across European Autonomic Centers. POTS emerged as the most frequently diagnosed new-onset CAD following SARS-CoV-2 infection or COVID-19 vaccination. The diagnostic work-up relies on a structured assessment, including a detailed medical (autonomic) history, neurological examination, active standing and/or head-up tilt testing, laboratory investigations to identify potential etiologic clues and exclude secondary causes or exacerbating factors, as well as more comprehensive (cardiovascular) autonomic function testing, where available. Individuals with post-COVID POTS frequently present with additional autonomic features, particularly thermoregulatory complaints and sudomotor dysfunction suggestive of a neuropathic subtype. An individualized, stepwise treatment approach progressing from non-pharmacological to pharmacological interventions, is recommended and can lead to symptomatic improvement in a substantial proportion of affected individuals.

Conclusion: A specialized diagnostic work-up is pivotal to diagnose or exclude CAD in individuals presenting with new-onset orthostatic intolerance following SARS-CoV2 infection or COVID-19 vaccination. Post-COVID POTS frequently present with additional autonomic features consistent with a neuropathic subtype. An individualized multimodal treatment strategy may result in symptomatic improvement in a substantial proportion of affected individuals.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.9 Fixing Perturbed Physiology: Dietary Salt And Compression To Treat Postural Orthostatic Tachycardia Syndrome (POTS)?

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Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by an increase in heart rate (≥30 bpm) within 10-minutes of upright posture, without orthostatic hypotension (>20/10 mmHg). In most cases, the increase in heart rate is thought to be secondary to a reduction in cardiac venous return, as evidenced by a reduction in stroke volume. Strategies to treat POTS by augmenting stroke volume include (1) increasing the blood volume, and (2) lower body compression to minimize the gravity-dependent fluid shifts that occur on standing.

In this presentation, we will review data on the efficacy of high dietary salt intake to increase plasma volume and blood volume in patients with POTS, and the downstream hemodynamic effects. We will then review a series of studies showing the effects of lower body compression and compression garments on hemodynamics in patients with POTS.

O.10 Impact of Age on Autonomic Symptoms and Quality-of-life in individuals with Orthostatic Intolerance: Postural Orthostatic Tachycardia Syndrome (POTS) vs. Postural Symptoms without Tachycardia (PSWT)

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Introduction: Individuals with Postural Orthostatic Tachycardia Syndrome (POTS) frequently present with severe autonomic symptom burden and poor health-related quality-of-life (HrQoL). Our understanding of symptoms and HrQoL in those with orthostatic intolerance (OI) who do not meet the strict heart-rate criteria for POTS, is poorly understood. While research has demonstrated regression of orthostatic tachycardia with aging, there are no age-based adjustments within the diagnostic criteria for POTS beyond ≤19 years. We compared autonomic symptoms and HrQoL in POTS compared to Postural Symptoms Without Tachycardia (PSWT); examining age-related effects on Delta heart-rate (DHR) and symptoms.

Methods: Consecutive patients undergoing OI assessment completed patient-reported outcome measures (PROMS) capturing autonomic symptoms and HrQoL. Between group comparisons utilised Chi-square for categorical variables and an independent t-test or Mann-whitney u-test for continuous variables as appropriate. Correlations between age, DHR, and PROMS were explored using Spearman's test. A secondary analysis was conducted utilizing age and sex-matching. Analyses used SPSS v29.0; significance set at $P< 0.05$.

Results: A total of 414 POTS and 151 PSWT participants were included (88.6% female in POTS vs. 89.4% female in PSWT; $P= 0.800$). Median age was lower in POTS (28 IQR 21–36) than PSWT (38 IQR 26–51; $P< 0.001$). Overall autonomic symptom burden (COMPASS-31) was similar between groups ($P= 0.349$), while those with POTS demonstrated worse OI (COMPASS-31 OI subdomain; $P = 0.005$) and HrQoL (EQ-Utility; $P= 0.019$) than PSWT. After age and sex-matching, these differences were no longer significant ($P> 0.05$). Weak-to-moderate negative correlations were seen between age and DHR ($r= -0.34$, $P< 0.001$) and age and total COMPASS-31 ($r =-0.11$, $P= 0.01$).

Conclusion: Comparable symptom burden and HrQoL in POTS and PSWT highlight limitations of DHR-based criteria. As orthostatic tachycardia declines with age, current diagnostic thresholds may require re-evaluation.

6TH Symposium - THE FAILING DIALOGUE: MOLECULAR AND CELLULAR DRIVERS OF CARDIAC AUTONOMIC DYSFUNCTION

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.21 Precise Nanomedicine Targeting Cardiac Sympathetic Afferents To Treat Chronic Heart Failure

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The cardiac sympathetic afferent reflex (CSAR) is a major contributor to sympathetic overactivation and progression of chronic heart failure (CHF) following myocardial infarction (MI). We hypothesized that MI initiates a neuroinflammatory cascade within thoracic dorsal root ganglia (DRGs) that sensitizes cardiopulmonary afferent pathways through suppression of voltage-gated potassium (Kv) channels, thereby exacerbating maladaptive autonomic reflexes.

Using a rat model of post-MI CHF, we found that thoracic DRGs exhibited time-dependent macrophage infiltration, satellite glial activation, increased expression of pro-inflammatory cytokines, and reduced Kv channel expression. Bulk RNA sequencing further demonstrated enrichment of macrophage activation and inflammatory signaling pathways within the DRGs. In vitro studies revealed that activated macrophages and pro-inflammatory cytokines directly suppressed Kv channel expression and increased DRG neuronal excitability, supporting a mechanistic link between neuroinflammation and afferent sensitization.

To determine whether suppression of neuroinflammation could mitigate these pathological changes, we first employed systemic oral minocycline treatment initiated three days before MI. Minocycline attenuated DRG inflammation, restored Kv channel expression, reduced exaggerated CSAR, and improved post-MI cardiac chamber remodeling. However, the systemic administration of anti-inflammatory agents is inherently limited by off-target effects and an inability to selectively target pathological peripheral neural circuits.

To overcome these limitations, we developed a precision nanomedicine strategy using a thermo-responsive hydrogel-based dexamethasone prodrug (ProGel-Dex) for local epidural delivery to thoracic DRGs. This sustained-release platform enabled selective modulation of peripheral neuroinflammation while minimizing systemic exposure and potential adverse effects associated with chronic corticosteroid therapy. A single administration of ProGel-Dex markedly reduced DRG neuroinflammation, restored Kv channel expression, normalized exaggerated afferent reflex responses, and improved cardiac chamber dilation for at least four weeks after MI.

Together, these findings identify peripheral neuroinflammation within thoracic DRGs as a critical driver of cardiopulmonary afferent sensitization and CHF progression after MI. Targeted suppression of DRG inflammation using sustained local nanomedicine delivery represents a promising precision therapeutic strategy to disrupt maladaptive neuro-cardiac signaling and improve outcomes in chronic heart failure.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.22 Precision Ultra-hypofractionated Radiotherapy To The Stellate Ganglia For Ventricular Arrhythmia (the First-in-man Radio-star Trial)

Benjamin Bussmann *(1)* ***- Ben George*** *(2)* ***- Maxwell Robinson*** *(3)* ***- James Grist*** *(4)* ***- Fintan Sheerin*** *(5)* ***- Ami Sabharwal*** *(2)* ***- Neil Herring*** *(1)*

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Introduction: Sympathetic activation is a hallmark of cardiac disease, contributing to disease progression and triggering ventricular arrythmias (VA). While implantable cardioverted defibrillators (ICD) improve mortality by terminating VAs, many patients experience recurrent ICD therapies, leading to worse outcomes and quality of life. Cardiac sympathetic denervation (CSD) through surgical removal of the stellate ganglia has emerged as an effective treatment for refractory VAs3 but carries a complication rate of up to 50%. We hypothesise that high precision image guided radiotherapy can be used to target the stellate ganglia to achieve CSD non-invasively leading to fewer complications while still maintaining efficacy.

Methodology: RADIO-STAR (ISRCTN 49861434, REC/SC/0005) is a phase 1 trial to establish the safety and feasibility of image guided radiotherapy to the stellate ganglia. 13 patients with structural heart disease who experience recurrent ICD therapy are invited to undergo image guided radiotherapy bilaterally to the lower half of the stellate ganglia and T1-2 sympathetic chain. Radiotherapy dose will be determined by a pre-specified dose escalation protocol. The primary outcome of this study is safety defined as any related severe adverse event (SAE) within 6 months of radiotherapy treatment. Secondary outcomes to evaluate feasibility and efficacy include ability to deliver radiotherapy and consequent changes in arrhythmia burden, circulating catecholamines, neuropeptide-Y, heart rate variability and structural changes in the stellate ganglia on MRI imaging.

Results: We have developed novel MRI and radiotherapy protocols to clearly visualise and accurately target the stellate ganglia. To-date 9 patients have completed radiotherapy treatment without related SAEs or significant side effects. Treatment has resulted in a reduction in arrhythmia burden.

Conclusions: Preliminary findings indicate that image guided radiotherapy to the stellate ganglia is feasible and safe. Completion of patient recruitment is required to evaluate efficacy.

Funding: British Heart Foundation (FS/CRTF/22/24437 and FS/SCRF/20/32005)

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.23 The Role Of Glial Cells In The Cardiac Autonomic Nervous System: The Missing Link For Nervous Hearts?

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The autonomic nervous system tightly regulates cardiac function in health and disease, and disruption of neuro-cardiac communication contributes to arrhythmias, heart failure and hypertension. While neurons have long been the focus of cardiac neuroscience, glial cells, which are indispensable for normal neuronal function throughout the central and peripheral nervous system, remain a comparatively overlooked component of the heart's autonomic architecture. Growing evidence suggests that glia accompany cardiac autonomic nerve fibers at all levels, from epicardial and endocardial innervation to intracardiac ganglia, yet their diversity, distribution and functional roles in the heart are only beginning to be understood. This talk aims to draw attention to glial cells as a potential "missing link" in the cardiac autonomic nervous system by highlighting their role health and cardiovascular disease.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.24 Head To Heart: Assessment Of Sympathetic Tone Using Sympathetic Vasomotion

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Introduction: The sympathetic nervous system is a key guardian of homeostasis, and dysfunction of this master regulator is a hallmark of cardiovascular and neurologic disease. Despite the importance of the sympathetic nervous system in health and disease, clinicians lack widely accessible measures of sympathetic outflow that can be deployed at the bedside. Our group has developed a novel measure of sympathetic vascular control, termed sympathetic vasomotion, that can be assessed through clinically available non-invasive measurements of blood flow and blood pressure.

Methods: Regional blood flow and systemic arterial pressure were measured in conscious rabbits, anesthetized pigs, and humans. Sympatholytic interventions, including surgical renal denervation, administration of intrathecal ropivacaine, catheter-based renal denervation, and lumbar sympathetic blockade, were performed. Normotensive hemorrhage was induced in conscious rabbits as a sympathoexcitatory stimulus. Sympathetic vasomotion was assessed by computing the time-varying arterial pressure-resistive blood flow transfer function.

Results: Sympathetic vasomotion reflected changes in sympathetic outflow in rabbits, swine, and man. Furthermore, sympathetic vasomotion exhibited a dose-response relationship with graded sympathomodulatory stimuli.

Conclusion: Sympathetic vasomotion allows for assessment of changes in regional sympathetic outflow. Further studies comparing sympathetic vasomotion with direct neural recordings and testing its utility in high-impact clinical scenarios are necessary.

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.11 Decoding Baroreflex Dysfunction After Spinal Cord Injury: Implications For Autonomic Dysreflexia

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Introduction: Cardiovascular dysfunction often occurs after high-level spinal cord injury (SCI). In this population, blood pressure instability contributes substantially to morbidity and mortality. The arterial baroreflex stabilizes hemodynamics through coordinated sympathetic and parasympathetic control. Following SCI, supraspinal regulation of sympathetic outflow is disrupted while parasympathetic pathways persist intact, resulting in autonomic imbalance and impaired baroreflex regulation of blood pressure. However, SCI-induced baroreflex dysfunction remains poorly understood in that clinical findings are variable and experimental animal models have rarely been examined.

Methods: To elucidate changes in baroreceptor-mediated cardiovascular and sympathetic reflexes following SCI, adult female rats underwent T4 spinal cord transection and survived for 4 weeks. After catheterization of the left femoral artery and vein, the cardiac baroreflex was assessed in conscious rats, while the sympathetic baroreflex was tested by recording splanchnic sympathetic nerve activity (sSNA) in Inactin-anesthetized rats. Mean arterial pressure (MAP) and heart rate (HR) were recorded simultaneously during phenylephrine (PE)-mediated pressor and sodium nitroprusside-mediated depressor challenge. To explore potential therapeutic strategies, a separate cohort of rats with crush SCI received embryonic brainstem-derived neural progenitor cell (NPC) transplantation and/or passive hindlimb cycling exercise training for 10 weeks. Subsequent to sympathetic baroreflex assessments, a sigmoidal reflex curve was generated using a four-parameter logistic model and then analyzed by nonlinear regression.

Results: Rats with intact spinal cords showed the expected inverse baroreflex relationships, in which increases in MAP were associated with decreases in both HR and sSNA. In SCI rats, the MAP-HR relationship was preserved but the curve became steeper, with a more negative gain, suggesting cardiac baroreflex hypersensitivity. During sympathetic baroreflex testing, strikingly, the MAP-sSNA relationship was disrupted and reversed, such that PE-mediated increases in MAP evoked sympathoexcitation rather than sympathoinhibition. Following cell- and/or rehabilitation-based treatments, both NPC transplantation and exercise partially improved baroreflex function.

Conclusion: High-level SCI alters both cardiac and sympathetic baroreflex function, producing cardiac baroreflex hypersensitivity and a reversed sympathetic response to blood pressure elevation. These maladaptive changes may contribute to the severe bradycardia and hypertension that characterize autonomic dysreflexia. NPC transplantation and exercise partially improve baroreflex function and may help restore cardiovascular stability after SCI.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.12 Strain Dependent And Chamber Specific Variations In Cardiac Cholinesterase Activity In Female Rats: Implications For Normotensive Controls And Hypertensive Models

Kissylla Brisson Da Silva (1)* - *Brayann Gonçalves Félix (1)* - *Gabriel Gavazza Noé (1)* - *Bruna Ferreira Da Silva (1)* - *Breno Lopes Macedo (1)* - *Maurício Da Silva Mattar (1)* - *Júlia Grigorini Mori Ayub (1)* - *Karla Nívea Sampaio (1)* - *Juliana Barbosa Coitinho (1)

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Introduction: Arterial hypertension is characterised by autonomic imbalance involving sympathetic hyperactivity and a withdrawal of parasympathetic protection. While the heart possesses an intrinsic nonneuronal cholinergic machinery that opposes hypertrophic signals, its regulatory enzymatic activity remains poorly defined in females. Previous studies from our group identified distinct chamber-specific activity in males and significant differences in circulating activity between Wistar, Wistar Kyoto (WKY), and spontaneously hypertensive rats (SHR) (unpublished observations). Given that female hearts exhibit unique electrophysiological properties and are underrepresented in autonomic research, this study compared compartmentalised cholinesterase activity in female Wistar, WKY, and SHR.

Methods: Adult female rats were divided into three groups: Wistar (N=14), WKY (N=15), and SHR (N=12). All experimental procedures were approved by the local Ethics Committee (CEUA Nº= 04/2024). Animals were euthanised by decapitation, hearts collected and dissected into four chambers: right atrium (RA), left atrium (LA), right ventricle (RV), and left ventricle (LV). Cardiac homogenates were used to assess ChE activity using Ellman's method. Total activity was measured in the absence of a butyrylcholinesterase (BChE) inhibitor, while specific AChEa was determined by BChE inhibition. Data were analysed by one-way ANOVA followed by the Tukey post hoc test. Differences were considered significant at $p<0.05$.

Results: Intracardiac enzymatic activity was highly compartmentalised and varied significantly by strain. In the RV, AChEa was significantly higher in SHR than in WKY females. Conversely, cholinesterasic activity was diminished in the RA of the hypertensive group compared to normotensive strains. WKY rats consistently displayed lower activity across chambers compared to both Wistar and SHR. Wistar rats exhibited a more stable and distinct cholinergic profile, supporting their role as a more consistent normotensive control for cardiovascular studies.

Conclusion Cardiac cholinesterase activity in females is strain-dependent and varies by heart chamber. These results emphasise that the choice of normotensive control is a critical variable in experimental design due to diverging cholinergic profiles between WKY and Wistar. Furthermore, identifying chamber-specific enzymatic differences in hypertensive females provides a basis for novel targeted therapeutic strategies to mitigate cardiac remodelling and failure while accounting for sexual dimorphism in autonomic regulation.

7TH Symposium - NEUROIMMUNE INTERACTION: HOW MUCH MORE DO WE HAVE TO DISCOVER?

TOPIC 04. Neuroimmune communication and neural control of immune responses

S.25 Peripheral Cellular-mediated Mechanism Of Sympathetic Anti-inflammatory Action

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Introduction. Bidirectional communication between the central nervous and immune systems is essential during immune challenges, enabling robust yet tightly regulated inflammatory responses that prevent collateral tissue damage.

This is largely mediated by the Splanchnic Anti-Inflammatory Pathway (SAIP) which runs in the sympathetic splanchnic nerves to limit inflammatory response following an immune challenge whilst promoting an anti-inflammatory pattern of cytokine release. Nevertheless, the exact immune cells directly involved in this anti-inflammatory signalling remain unclear.

Methods. To investigate this, selective immune cell depletion strategies were employed. Neutrophil depletion was obtained injecting intraperitoneally (i.p.) female and male CatchupIVM mice with an anti-Ly6G antibody (Ab-Ly6G; 200 mg/kg), twice in the 24 hours prior to surgery. Control animals received an isotype antibody (Ab-Iso) i.p. injection. Macrophage depletion was obtained in female and male Cx3Cr1GFP/+ mice with a single i.p. injection of liposomal clodronate (CLL; 25 µg/mouse) three days before the surgery. Control mice were i.p. injected with empty liposomes (COL). On experimental day, anesthetized mice were randomly assigned to either bilateral splanchnic nerve surgical resection (SplancX), for disabling the SAIP, or a sham-operation (Sham). All animals were then challenged with intravenous lipopolysaccharide (50 µg/kg). Blood samples were collected 90 minutes later to quantify circulating cytokines: tumor necrosis factor (TNF) and Monocyte Chemoattractant Protein-1 (MCP-1), both pro-inflammatory, and interleukin-10 (IL-10; anti-inflammatory).

Results. SplancX groups showed increased TNF and reduced IL-10 levels compared with Sham, confirming the anti-inflammatory role of the SAIP in both Ab-Iso (TNF 128.14±23.76 vs 70.65±19.50; IL-10 8.37±1.01 vs 23.42±2.78 ng/ml) and COL (TNF 186.90±56.45 vs 155.30±20.39; IL-10 11.64±3.22 vs 16.11±1.93 ng/ml). No significant difference was observed for MCP-1. In both Ab-Ly6G and CLL, the difference in TNF and IL-10 between Sham and SplancX groups was abolished (Ab-Ly6G: TNF 68.81±13.37 vs 87.77±22.75; IL-10 17.70±0.66 vs 13.62±3.27 ng/ml; CLL: TNF 21.44±6.58 vs 21.42±2.83; IL-10 3.34±0.94 vs 7.14±3.40 ng/ml). Notably, macrophage depletion markedly reduced overall cytokine levels.

Conclusion. These findings suggest that both neutrophils and macrophages contribute to mediate the anti-inflammatory action of the SAIP. Furthermore, macrophages appear to be the principal source of cytokines during an inflammatory challenge.

TOPIC 04. Neuroimmune communication and neural control of immune responses

S.26 Vagal Regulation Of Adrenergic Tone Impacts Effective Antiviral Immunity In The Central Nervous System

Kaitlin Murray (1) *- Pouya Khosravi (1) - Alexander Murray (1) - Lucas Le (1) - Miguel Santos (1) - Rijul Malik (1) - Brianna Min (1) - Kellie Fernandez (1) - Jessica Breslin (1) - Thomas Lane (1)*

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The autonomic nervous system coordinates peripheral immune responses, but whether it shapes antiviral defense within the central nervous system (CNS) remains poorly understood. Vagal signaling operates in counterbalance with sympathetic adrenergic outputs, and catecholamines modulate myeloid and lymphoid function through β2-adrenergic receptors (β2-AR). However, whether endogenous vagal tone regulates CNS antiviral immunity during neuroinflammatory disease is unknown.

To address this, mice underwent left cervical vagotomy (VGX) 14 days prior to intracranial inoculation with the neurotropic JHM strain of mouse hepatitis virus (JHMV), a well-characterized model of viral encephalitis. Immune responses were assessed by flow cytometry at days 3 and 7 post-infection, and spatial transcriptomics was performed to resolve spatially organized changes in glial and immune cell states within the brain.

VGX mice exhibited increased viral burden accompanied by reduced expression of inflammatory mediators — including Ifnγ, Cxcl9, and Cxcl10 — despite largely intact early innate immune infiltration. By day 7, accumulation and effector function of virus-specific $CD8^+$ T cells were significantly diminished in VGX brains. Spatial transcriptomic analysis revealed that VGX selectively suppressed microglial antigen presentation programs, including reduced MHC class II expression and downregulation of chemokines critical for T cell recruitment, without broadly altering CNS cellular composition. Circulating catecholamines were elevated in JHMV+VGX mice, implicating a shift in autonomic balance toward excess adrenergic tone. Pharmacologic antagonism of β2-AR fully restored microglial activation, T cell accumulation and effector function, and viral control in VGX mice.

These findings identify a vagal-adrenergic neuroimmune axis that actively shapes the magnitude and quality of antiviral immunity in the CNS. Disruption of vagal signaling, as occurs during illness, surgery, or autonomic dysfunction, elevates catecholamine tone, suppresses microglial inflammatory programs via β2-AR, and compromises $CD8^+$ T cell-mediated viral clearance. This work reveals a previously unrecognized neural circuit governing neurological host defense.

S.27 TNF-α drives carotid body and autonomic dysfunction in dysmetabolic states: reversal through anti-inflammatory modulation

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The carotid body (CB) is a key peripheral chemosensory organ involved in the regulation of cardiorespiratory and autonomic function. Beyond its classical role in oxygen sensing, evidence indicates that the CB is sensitive to metabolic and inflammatory signals contributing to obesity and metabolic disease. In this talk, I will discuss evidence supporting a neuroimmune mechanism linking metabolic dysfunction to CB and autonomic dysregulation, with a particular focus on the contribution of TNF-α signaling within the CB and its potential reversibility through anti-inflammatory modulation.

Using experimental models of diet-induced obesity and metabolic dysfunction, we investigated structural, molecular and functional changes within the CB and their impact on chemoreflex regulation. Obesity was associated with activation of a local inflammatory phenotype in the CB, characterized by increased TNF-α expression and macrophage accumulation, accompanied by enhanced CB tonicity and chemosensory activity. To investigate whether inflammatory signaling contributes causally to these adaptations, we tested whether pharmacological anti-inflammatory treatment with ibuprofen could reverse obesity-induced CB and metabolic dysfunction. Chronic ibuprofen treatment reduced CB inflammation, decreased TNF-α expression and macrophage infiltration, normalized basal carotid sinus nerve activity, improved insulin sensitivity, and preserved physiological chemosensory responses.

These findings identify TNF-α as a key contributor to CB dysfunction in obesity and show that anti-inflammatory treatment restores CB function while improving metabolic homeostasis.This broaden our understanding of the neuroimmune-metabolic interactions occurring within the CB and support its role as an integrator of metabolic and inflammatory signals that contribute to sympathetic and metabolic dysfunction during obesity.

TOPIC 04. Neuroimmune communication and neural control of immune responses

S.28 Human Cadaveric Tissues: A Critical Bridge For Translational Neuro-immune Research

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Introduction: Translation of neuro-immune discoveries into clinical applications is challenging by the limited availability of human tissues that accurately reflect native human anatomy and cellular interactions. However, through our department's body donation program, we have continuous access to a diverse range of high-quality post-mortem tissues, creating opportunities to study the human neuro-immune interface and identify potential targets for therapeutic modulation. We evaluated the applicability of multiple methodologies in post-mortem tissues to characterize nerves, immune cell populations, receptors, and associated structures such as ganglia and show that human cadaveric tissues provide a unique platform to bridge this translational gap, enabling direct investigation of neuro-immune structures and pathways in their physiological human context. Here we summarize key findings, discuss methodological considerations, and highlight emerging opportunities for functional and translational applications of human cadaveric tissues in neuro-immune research.

M&M: Formaldehyde-fixed human cadaveric tissues (e.g., spleen, lymph nodes, serosa, mucosa and ciliary body) were studied for neuro-immune features (nerves, immune cells, and receptors) using detailed dissections and microscopic techniques on both sections and whole mounts. Microscopic imaging was performed with brightfield, fluorescence, and light sheet microscopy and subsequent morphometric and image analysis methods were applied. Pilot studies with external collaborators explored functional applications, including RNAscope and the development of cell cultures and organoids from tissues with short post-mortem intervals.

Results: We showed that all examined lymphoid structures contained primarily sympathetic nerves near immune cells like T cells and macrophages, which express β2-adrenergic receptors, indicating a neuro-immune regulatory interface. Light sheet microscopy of whole mounts offered superior 3D visualization over tissue sections. Dissection followed by nerve analysis identified potential neuromodulatory targets. Additionally, post mortem tissues can be used for RNAscope and cell /organoid cultures.

Conclusion: Our results support the existence of a neuro-immune interface in human lymphoid and peripheral tissues and demonstrate that RNAscope proved effective in detecting gene activity, and viable cells and tissues could still be cultured post mortem. Collectively, these results suggest cadaveric tissues are not only suitable for anatomical but also functional studies, such as assessing immune cell behavior in ex vivo models.

TOPIC 04. Neuroimmune communication and neural control of immune responses

O.13 Brain Regions Regulating Systemic Inflammation

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Introduction. The splanchnic sympathetic nerves exert a strong inhibitory influence on systemic inflammation by suppressing the secretion of inflammatory cytokines e.g. tumor necrosis factor-α (TNF) and stimulating release of anti-inflammatory interleukin-10 into the circulation. Our aim was to identify CNS pathways that regulate this splanchnic anti-inflammatory pathway (SAIP). Methods. To determine which CNS regions are involved, we investigated whether transecting the neuraxis at different levels from spinal cord to hypothalamus increased plasma TNF in response to intravenous lipopolysaccharide (LPS, 60ug/kg i.v.) at 75 or 90 minutes after its injection, compared with sham operated rats (Shams), and if it did so, whether bilaterally cutting splanchnic nerves (SNX) caused any further increase. Urethane anesthetized Sprague Dawley male rats, both intact and adrenalectomized (to remove anti-inflammatory glucocorticoid influences), were studied. Results. Transecting the cervical (C3) spinal cord in normal rats caused plasma TNF response to LPS to increase (21.5±10.6 vs. 3.1±1.8 ng/ml in Shams, $p<0.01$), similar to the increase caused by SNX alone. SNX in transected rats caused no further increase, indicating supraspinal regulation of the SAIP. Transection of caudal medulla increased plasma TNF responses to LPS (27.3±13.7 vs 7.6±5.3 ng/ml in Shams; $p<0.01$, n = 5 each). No further increase occurred with SNX, suggesting that the SAIP was disabled by these transections. Transection just rostral to the medulla did not increase TNF responses (4.3±2.2 vs. 6.8±2.2 ng/ml in Shams, n = 4), indicating that the SAIP was intact and its premotor neurons were located in the medulla. Similar pre-medullary transection or mid-brain transection in adrenalectomized rats, caused plasma TNF responses to be less than in sham operated rats, and also less than those with pre-medullary or midbrain transection plus SNX, suggesting that although the SAIP remained intact, a distinct pro-inflammatory influence may have been disrupted, reducing the plasma TNF response. Conclusion. These results show that the pre-motor neurons driving the Splanchnic anti-inflammatory pathway are likely to be located in the medulla oblongata. They also suggest that regions rostral to the medulla may exert pro-inflammatory influences on responses to LPS.

TOPIC 04. Neuroimmune communication and neural control of immune responses

O.14 Contribution Of ß2-adrenergic And Neuropeptide Y-type 1 Receptors To The Anti-inflammatory Effects Mediated By The Inflammatory Reflex

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Introduction: The inflammatory reflex is a neuroimmune mechanism through which the nervous system modulates inflammatory responses to pathogen invasion and tissue injury. Its efferent arm is conveyed via sympathetic fibres that are located within the greater splanchnic nerves and innervate abdominal organs. Endogenous activation of this reflex suppresses inflammation through the release of adrenaline from the adrenal medulla into the circulation, as well as noradrenaline and neuropeptide Y (NPY) from postganglionic sympathetic neurons into local tissues. These key mediators of sympathetic immunomodulation exert their effects through receptors expressed on immune cells. Here, we investigated the contribution of β2-adrenergic receptors (β2ADRs) and NPY receptor type 1 (NPY1Rs) to the anti-inflammatory actions of the inflammatory reflex.

Methods: β2ADRs knockout (β2ADRs-KO), NPY1Rs knockout (NPY1Rs-KO), and wild-type (WT) C57BL/6J mice underwent bilateral splanchnic denervation (SplancX) or sham surgery, followed by lipopolysaccharide injection (LPS, 50 µg/kg, i.v.). After 90 minutes, plasma levels of the pro-inflammatory cytokine tumor necrosis factor-α (TNF) and the anti-inflammatory cytokine interleukin-10 (IL-10) were measured. The inflammatory response was compared between sham and SplancX animals within each genotype; loss of the denervation effect indicates that the receptor is required for the anti-inflammatory action of the inflammatory reflex.

Results: In line with previous findings, splanchnic denervation in WT mice increased plasma TNF and decreased IL-10 levels. In β2ADRs-KO mice, TNF levels did not differ significantly between Sham and SplancX groups; whereas IL-10 concentrations remained lower in SplancX than in Sham animals. In contrast, NPY1Rs-KO mice exhibited responses comparable to those observed in WT animals, with splanchnic denervation increasing TNF and decreasing IL-10 levels relative to sham-operated controls.

Conclusion: These findings suggest that β2ADRs contribute to the inhibitory effect of the inflammatory reflex on TNF production during systemic LPS challenge but are not required for the regulation of IL-10 levels. In contrast, NPY1Rs do not appear to play a major role in the anti-inflammatory actions mediated by the splanchnic sympathetic nerves.

8TH Symposium - AUTONOMIC DYSFUNCTION IN NEURODEGENERATIVE DISORDERS: FROM MECHANISMS TO THERAPIES

(In collaboration with ABBVIE)

TOPIC 11. Emerging Concepts And Novel Perspectives In Autonomic Neuroscience

S.29 Mechanisms Of Neurodegeneration In Synucleinopaties

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Although the discovery of the critical role of α-synuclein (α-syn) in the pathogenesis of Parkinson's disease (PD) is now twenty-five years old, it still represents a milestone in PD research. Abnormal forms of α-syn trigger selective and progressive neuronal death through mitochondrial impairment, lysosomal dysfunction, and alteration of calcium homeostasis not only in PD but also in other α-syn-related neurodegenerative disorders such as dementia with Lewy bodies, multiple system atrophy, pure autonomic failure, and REM sleep behavior disorder. Furthermore, α-syn-dependent early synaptic and plastic alterations and the underlying mechanisms preceding overt neurodegeneration have attracted great interest. In particular, the presence of early inflammation in experimental models and PD patients, occurring before deposition and spreading of α-syn, suggests a mechanistic link between inflammation and synaptic dysfunction. The knowledge of these early mechanisms is of seminal importance to support the research on reliable biomarkers to precociously identify the disease and possible disease-modifying therapies targeting α-syn.

The recent "NSD-ISS" and "SynNeurGe" research frameworks have proposed new biological diagnostic criteria focusing on α-synucleinopathy, neurodegeneration, and genetic biomarkers, independent of clinical manifestations. These proposals intend to detect the disease at a "biologically early phase" to foster advances in research and development of disease-modifying treatments. While the shift to a biological approach is mandatory to better understand PD, challenges to the new frameworks remain, including inherent criticisms, limitations in explaining PD clinical-biological complexity, restricted clinical applicability and related ethical concerns. In this paper, we describe the historical path toward the two biological proposals, explore critical issues and knowledge gaps emerging from them, and discuss the risk of their premature application in the clinical setting.

S.29 Autonomic Dysfunction in Neurodegenerative Disorders

Valeria Iodice (University College London Hospital, UK)

S.30 Symptomatic and Disease-Modifying Treatments in Neurodegenerative Disorders

Alessandra Fanciulli (Medical University of Innsbruck, Austria)

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.15 Pure Autonomic Failure: A Peripheral Neurodegenerative Disease With High Risk Of Phenoconversion To Central Synucleinopathy

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Introduction: Pure autonomic failure (PAF) is a neurodegenerative disorder characterized by phosphorylated alpha-synuclein (P-SYN) deposition within peripheral nerves. PAF is considered a prodromal disease state with high rates of phenoconversion to a central synucleinopathy (Parkinson's disease, PD; multiple system atrophy, MSA; dementia with Lewy bodies, DLB) over 20 years. As novel disease-modifying therapies for synucleinopathies are developed, early detection is crucial.

Methods: Thirty-three patients with a clinical diagnosis of PAF were enrolled. Detailed history, examinations, and questionnaires were completed. A medical record review by an expert panel confirmed PAF diagnosis. Skin biopsies were performed at standard sites. Biopsies were immunostained for protein gene product 9.5 and P-SYN. Intra-epidermal and autonomic nerve fiber densities and P-SYN deposition were measured for each biopsy. Follow-up information for a subset of patients was available through routine clinical care.

Results: Of the 33 recruited patients, 22 were 'clinically confirmed' as PAF by the expert panel. The remaining 11 were excluded, either showing features of phenoconversion or misdiagnoses. P-SYN was detected in 22/22 (100%) of clinically confirmed PAF and 10/11 (91%) of the excluded patients. IENFD was reduced at the distal leg in 17/22 (77%) of the clinically confirmed patients and in 8/11 (73%) of the excluded patients. Follow-up with the recruiting sites revealed that of those with clinically confirmed PAF, 5/14 (36%) phenoconverted to synucleinopathy (n=2 DLB, n=1 PD, n=2 MSA) over 4 years. Of the excluded patients, 7/9 (78%) converted to a synucleinopathy (n=5 DLB, n=1 PD, n=1 progressive supranuclear palsy) over the same time period. Both patients who converted to MSA had subepidermal plexus P-SYN deposition, and one was autopsy confirmed.

Conclusion: Skin biopsy detection of alpha-synuclein has high diagnostic sensitivity and specificity in PAF patients. High rates of phenoconversion are noted over 4 years of follow-up, particularly in those with subtle features of a central synucleinopathy. Skin biopsy offers a simple tool to simultaneously detect P-SYN and nerve fiber densities that could aid in predicting development of MSA in patients with suspected PAF. The results of this study support the study of PAF patients as a prodromal synucleinopathy in disease modifying trials.

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.16 Combined Cardiovascular Autonomic Failure And Cognitive Impairment As Independent And Additive Predictors Of Progression And Phenoconversion In Isolated REM Sleep Behavior Disorder

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Introduction and objectives: Isolated REM Sleep Behavior Disorder (iRBD) is a prodromal state of α-synucleinopathies, in which early identification of high-risk individuals remains a clinical challenge. While cardiovascular autonomic failure (cAF) and cognitive impairment (CI) are established biomarkers of disease progression, their combined prognostic significance has not been fully explored. This study aimed to: (1) explore the cross-sectional and longitudinal interplay between autonomic and cognitive dysfunctions in iRBD; (2) assess their respective and combined roles in predicting phenoconversion.

Methods: Seventy-four iRBD patients (73% male, mean age at onset 62.2±8.1 years) were prospectively recruited and followed annually (mean follow-up:3.17±1.88 years). All underwent cardiovascular reflex testing (CRT), including Tilt Table Test, Valsalva Maneuver, Deep Breathing, Cold Face, and Handgrip tests, plus a standardized neuropsychological battery. Cognitive and autonomic changes were assessed cross-sectionally and longitudinally. Survival analyses (Kaplan-Meier and Cox regression) estimated phenoconversion risk.

Results: At baseline, 17 patients (25.4%) had mild cognitive impairment (MCI), and 12 (17.9%) exhibited neurogenic orthostatic hypotension (nOH). No significant association was found between CI and nOH either cross-sectionally (MCI prevalence:33.3% with nOH vs23.6% without; p=0.484) or longitudinally. Over time, MCI with multiple-domain involvement increased significantly (OR=1.65, 95%CI:1.02-2.66; p=0.038), with deterioration in visuospatial (OR=1.17, 95%CI:1.07-1.28; p=0.001) and memory domains (OR=1.50, 95%CI:1.00-2.25; p=0.050). Meanwhile, nOH progressed significantly with time (e.g., OH at 3min:OR=1.66, 95%CI:1.06-2.60; p=0.026). Fifteen patients (20.3%) phenoconverted (6 to DLB, 5 to PD, 2 to MSA, 2 to unspecified atypical parkinsonism) over mean follow-up 3.17±1.88 years. Cox regression revealed that both MCI (HR=3.71, 95%CI:1.22-11.22; p=0.020) and nOH (HR=3.64, 95%CI:1.20-10.98; p=0.022) independently increased conversion risk. Their concomitant presence amplified the hazard ratio to 12.12 (95%CI:2.76-53.29; p=0.001), indicating a four-fold higher risk than either factor alone.

Conclusions: In iRBD, cognitive and autonomic dysfunctions follow parallel but independent progression pathways. While they do not significantly influence each other in their evolution, their coexistence markedly enhances the risk of developing α-synucleinopathies. These findings support a multidimensional biomarker model integrating autonomic and cognitive assessments to improve phenoconversion risk stratification and patient monitoring in prodromal α-synucleinopathies.

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.17 Autonomic Failure In Patients With IgLON5 Disease: Broadening The Spectrum

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Introduction: Anti-IgLON5 disease is a rare disorder that combines neurodegeneration and autoimmunity. Clinically, it may present with a combination of bulbar symptoms, sleep disturbances, movement disorders, and dysautonomia, which can make early recognition challenging and may lead to confusion with more common conditions, particularly alpha-synucleinopathies. In this study, we present the first objective characterization of autonomic nervous system dysfunction in patients with anti-IgLON5 disease, comparing them with subjects with idiopathic REM sleep behavior disorder –iRBD- and control individuals.

Methods: We conducted a cross-sectional study including 12 patients with anti-IgLON5 disease, 12 age- and sex-matched iRBD patients, and 12 matched controls. All participants underwent standardized autonomic reflex testing, including deep breathing, Valsalva maneuver, and active standing with continuous blood pressure and ECG monitoring. Cardiovagal and sympathetic adrenergic functions were quantified using the Composite Autonomic Severity Score. Autonomic symptoms were assessed with COMPASS-31.

Results: Cardiovagal dysfunction was present in 63.6% of anti-IgLON5 patients and 41.6% of iRBD patients, with significantly lower heart rate variability and Valsalva ratio compared to controls ($p<0.05$). Anti-IgLON5 patients showed the most pronounced impairment. Adrenergic dysfunction was also observed, with reduced phase IV blood pressure overshoot in both patient groups versus controls ($p=0.001$), but no significant differences between anti-IgLON5 and iRBD. No correlation was found between autonomic dysfunction severity and disease duration. COMPASS-31 scores did not differ significantly between patient groups.

Conclusion: Autonomic dysfunction is highly prevalent in anti-IgLON5 disease, affecting both cardiovagal and adrenergic domains. Its overlap with iRBD suggests shared pathophysiological mechanisms, while more severe cardiovagal impairment might distinguish anti-IgLON5 disease. Early recognition of autonomic involvement may facilitate timely diagnosis and treatment.

HOT TOPIC SESSION

TOPIC 04. Neuroimmune communication and neural control of immune responses

O.18 Premotor Neurons Of The Splanchnic Anti-inflammatory Pathway

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Introduction: The central nervous system exerts strong reflex control of systemic inflammation via the splanchnic anti-inflammatory pathway (SAIP). In response to systemic immune challenge, this sympathetic nerve pathway suppresses the resultant release of the key pro-inflammatory cytokine tumor necrosis factor-α (TNF) while enhancing levels of the anti-inflammatory cytokine, interleukin-10. The effectiveness of the reflex may be measured by the excess TNF levels in animals with cut splanchnic nerves versus sham-operated controls, 75 mins after challenge with lipopolysaccharide (LPS, 60ug/kg i.v.). Transection experiments (McKinley et al., this meeting) indicate that the sympathetic premotor neurons of the SAIP are located in the medulla.

Methods: In two series of experiments measuring plasma TNF responses to LPS in urethane-anaesthetized rats, we compared the effect of inhibiting medullary premotor cell groups with bilateral stereotaxic microinjections of the GABA-A agonist, muscimol (0.2 mM), with simply cutting the splanchnic nerves. In a third series, we used Fos immunohistochemistry on perfusion-fixed brains to determine which neurons with projections to the lower thoracic spinal cord (retrogradely labelled following spinal injection of cholera toxin subunit b, made one week beforehand) were activated by i.v. LPS in the conscious animal.

Results: Bilateral injections of 200nl muscimol into either the rostral ventrolateral medulla (RVLM) or rostral ventromedial medulla (RVMM) were effective in raising the plasma TNF response to LPS in animals with intact splanchnic nerves. Smaller injections (50 nl) into either nucleus also raised plasma TNF responses, but failed to show any clear difference between the two nuclei. Injections into the medullary raphé were ineffective, however. Following LPS challenge, a greater proportion of spinally-projecting neurons in RVLM expressed Fos than was the case in RVMM (52% vs. 30%: n=2 rats). Saline control injections gave 14% and 15%, respectively (n=3 rats). In LPS-treated rats, one third of the Fos-activated RVLM neurons also expressed tyrosine hydroxylase.

Conclusions: The premotor neurons for the SAIP are likely located in the RVLM and maybe also in the RVMM, but not in the medullary raphé. Both C1 and non-C1 neurons are implicated.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.19 The Association Between Obesity And The Functions Of The Autonomic Nervous System In Young Adults

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Obesity is one of the most prevalent public health issues. Excess weight has been associated with autonomic dysfunction, but the evidence in young adults is scarce. Therefore, this study aims to assess the relationship between the body mass index (BMI) and the autonomic nervous system (ANS) function in young adults. Males are known to have higher sympathetic nervous system activity as compared to females, who are known to have a greater parasympathetic function. Hence, it is critical to assess the differences in ANS activity based on gender. This study was done on 120 university students aged 18 - 25 years, categorized based on BMI as normal (18kg/m2-24kg/m2) and obese (>25kg/m2). The ANS function was assessed by performing the Isometric Handgrip Test (IHGT), Deep Breathing Test (DBT), and Cold Pressor Test (CPT). Our study revealed that obese individuals exhibited an increase in the blood pressure and heart rate as compared to normal individuals, indicating that the former might be at greater risk for the development of ANS dysfunction. Our study also revealed that obese males exhibited a greater change in their blood pressure as compared to their obese counterparts.

TOPIC 07: Molecular and systems-level mapping of autonomic circuits and brain–body integration

O.20 Maternal Accuracy In Perceiving Fetal Movements: Influence Of Mental Health And Interoceptive Abilities — A Pilot Study

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Introduction: Fetal movement counting (FMC) is routinely used in clinical practice as an indicator of fetal well-being. However, FMC relies on the pregnant woman's subjective perception of fetal movements, referred to here as fetoception. We hypothesized that maternal fetal perception accuracy (MFPA) shows substantial interindividual variability during non-pathological pregnancies. This study aimed to quantify MFPA and explore factors potentially explaining this variability, including maternal mental health, interoceptive abilities and heart rate variability (HRV).

Methods: In this clinical research protocol conducted within standard care and approved by the ethics committee, participants underwent a 30-minute cardiotocography recording. Fetal heart rate activity, used as a proxy for fetal movements, was recorded while participants pressed a button whenever they perceived a fetal movement. MFPA was quantified using an F1-score. Maternal mental health was assessed using validated questionnaires evaluating depressive symptoms (EPDS, BDI, MADRS), anxiety (STAI-trait, STAI-state, PRAQ-R2), and sleep quality (ISI). Interoceptive abilities were evaluated using MAIA and THISQ questionnaires, complemented by ECG-derived vagal heart rate variability (HRV) as an objective marker of autonomic nervous system functioning. Maternal–fetal attachment was measured using the PAI questionnaire.

Results: Thirteen pregnant women followed at Saint-Maurice Hospitals have been included to date. F1-scores ranged from 0.04 to 0.71 (mean = 0.38; coefficient of variation = 0.58), indicating marked variability in MFPA. MFPA was negatively correlated with depressive symptoms and positively correlated with maternal–fetal attachment and HRV. Exploratory analyses revealed associations between depressive symptoms, insomnia, reduced interoceptive non-distraction, and lower maternal–fetal attachment.

Conclusion: This pilot study demonstrates substantial variability in maternal fetal perception accuracy. Associations with mental health and interoceptive processes, associated with cardiac vagal function, suggest new research perspectives in perinatal care and maternal–fetal interaction.

TOPIC 11. Emerging concepts and novel perspectives in autonomic neuroscience

O.21 Intestinal Vagal Serotonin Signaling Links Gut Dysbiosis To Hypertension

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Introduction: Gut dysbiosis is increasingly implicated in hypertension, but the neural mechanisms linking intestinal microbes to blood pressure dysregulation remain unclear. Intestinal serotonin (5-HT) and vagal afferents expressing 5-HT3a receptors are positioned to relay microbiota-dependent signals to cardiovascular control circuits. Methods: The study combined fecal microbiota transplantation, targeted metabolomics, radiotelemetry, in vivo calcium imaging, and intersectional viral approaches in normotensive Wistar-Kyoto (WKY) rats, spontaneously hypertensive rats (SHR), and transgenic 5HT3aCre-derived models. Hypertensive or normotensive microbiota were transferred into antibiotic-treated recipients, followed by longitudinal blood pressure monitoring and measurements of colonic 5-HT signaling. 5-HT3aR-expressing vagal afferents, including colon-projecting subsets, were selectively stimulated, ablated, or restored to define their role in blood pressure regulation. Human colonic biopsies from hypertensive and normotensive subjects were also analyzed for 5-HT, Tph1, and 5-HT3aR expression. Results: Transfer of hypertensive microbiota increased blood pressure and reduced colonic 5-HT and Tph1 expression in recipient rats, consistent with impaired host intestinal 5-HT production. Hypertensive rodents also showed reduced 5-HT3aR expression along the vagal gut-brain axis and blunted depressor responses to 5-HT3aR stimulation. Selective activation of 5-HT3aR vagal afferents rapidly lowered blood pressure, whereas ablation of these neurons caused progressive hypertension and worsened stress-related pressor responses. Conversely, restoring 5-HT3aR expression in colonic vagal afferents attenuated hypertension in dysbiotic rats, and dietary tryptophan further enhanced this effect by increasing colonic 5-HT. Human subjects with hypertension similarly exhibited reduced colonic 5-HT, Tph1, and 5-HT3aR expression, proving translational relevance. Conclusion: Intestinal 5-HT-dependent vagal 5-HT3aR signaling is a microbiota-sensitive pathway required for blood pressure homeostasis and is impaired in experimental and human hypertension. This axis represents a clinically relevant therapeutic target for dysbiosis-associated and treatment-resistant hypertension. Disclosure: Jasenka Zubcevic is co-founder of Panthea Life.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.22 Beyond The Baroreflex: A Prefrontal-thalamic-brainstem Network Preceding Spontaneous Sympathetic Burst Generation

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Muscle sympathetic nerve activity (MSNA) is a direct measure of sympathetic vasoconstrictor outflow classically associated with arterial baroreflex-mediated blood pressure regulation. However, the central neural mechanisms preceding spontaneous MSNA burst generation remain poorly understood. We combined magnetoencephalography, magnetic resonance imaging, and microneurography to identify cortical, subcortical, and brainstem activity associated with the occurrence or absence of spontaneous MSNA bursts during resting wakefulness.

Nineteen healthy adults (age 30 ± 10 years; BP 109 ± 11 / 73 ± 8 mmHg; HR 70 ± 11 bpm) underwent simultaneous microneurography and whole-brain neuroimaging during 10 minutes of quiet rest. Epochs were defined using each participant's mean R-R interval duration, with the R-wave peak set as t = 0. Each epoch was classified as burst or no-burst according to MSNA activity in the subsequent R-R interval, accounting for the ~1-second central-to-peripheral conduction delay. Equal numbers of burst and no-burst epochs were contrasted across source-localised spectral power, phase-amplitude coupling, and amplitude-envelope connectivity spanning seven frequency bands (0.5–120 Hz). Since both conditions were anchored to the same cardiac cycle framework, differences reflected central neural correlates of MSNA burst generation rather than cardiac timing or baroreflex gating. Cortical, subcortical, and brainstem regions were defined using the HCP-MMP, CIT168, and Brainstem Navigator probabilistic atlases respectively.

Mean resting MSNA burst incidence was 41.6 ± 16.7 bursts per 100 heartbeats, with blood pressure and heart rate stable throughout. Spectral analyses revealed alpha- and beta-band source power in brainstem regions consistent with the left lateral parabrachial nucleus and periaqueductal grey. Gamma-band activity was identified within the left frontal pole (Brodmann Area 10), implicated in higher-order cognitive and interoceptive integration. Significant beta-to-gamma phase-amplitude coupling between brainstem and frontopolar clusters suggested cross-frequency coordination between pontine autonomic nuclei and higher cortical areas preceding burst generation. Amplitude-envelope connectivity revealed increased node strength in the right mediodorsal thalamic nucleus, with white matter tract analysis indicating spatial association with the corticospinal tract.

Frontopolar, thalamic, and pontine brainstem dynamics precede spontaneous MSNA bursts during rest. These findings support a model in which sympathetic outflow emerges from coordinated higher-order cortical-autonomic network activity rather than solely from beat-to-beat baroreflex mechanisms.

TOPIC 04. Neuroimmune communication and neural control of immune responses

O.23 Splanchnic Denervation Enhances Bacterial Clearance During Streptococcus Pneumoniae Infection

Elisa De Angelis (1)* - *Zuzana Tonelli Gombalova (1)* - *Alessandra Occhinegro (2)* - *Luca Alberti (1)* - *Simona Quaglietta (1)* - *Emiliana Piscitiello (1)* - *Timna Hitrec (1)* - *Matteo Cerri (1)* - *Marco Luppi (1)* - *Domenico Tupone (1)* - *Roberto Amici (1)* - *Claudia Trappetti (3)* - *Marco Rinaldo Oggioni (3)* - *Robin Mcallen (2)* - *Michael Mckinley (2)* - *Davide Martelli (1)

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Background: The inflammatory reflex (IR) is an endogenous neural mechanism that modulates innate immunity. Its efferent arm travels through the splanchnic sympathetic nerves and suppresses inflammatory responses during immune challenge. Bilateral splanchnic denervation enhances bacterial clearance during Gram-negative infection, suggesting that the IR restrains antibacterial host defence. Whether this mechanism also operates during infection with Gram-positive pathogens remains unclear. We investigated the impact of splanchnic denervation on bacterial clearance during systemic infection with Streptococcus pneumoniae.

Methods: Female CD-1 wild-type mice underwent either bilateral splanchnic denervation (SplancX; n = 5) or sham surgery (n = 6) under deep anaesthesia. Following one week of recovery, mice received an intravenous inoculation of S. pneumoniae D39 (1×10^5 CFU). Blood samples were collected by cheek bleed at 1, 6 and 24 h post-infection for quantification of circulating bacteria.

Results: No detectable bacteremia was observed in SplancX mice at any time point. In contrast, bacteremia was detected in 4/6 Sham animals at both 1 h and 24 h after infection. Bacterial loads were significantly higher in Sham mice than in SplancX mice at 24h (adjusted p = 0.041). No bacteremia was detected in either group at 6 h. These preliminary results suggest that the SplancX group has an improved ability to control systemic S. pneumoniae infection.

Conclusions: Bilateral splanchnic denervation enhanced bacterial clearance during systemic S. pneumoniae infection. These findings support the hypothesis that the inflammatory reflex suppresses antibacterial immune mechanisms and extend previous observations obtained during Gram-negative infection to a clinically relevant Gram-positive pathogen. Further studies are required to define the underlying mechanisms and determine the impact on disease outcome.

9TH Symposium - ELECTROCEUTICALS FOR CONTROLLING CARDIORESPIRATORY DISEASES

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.31 Bionic Pacemaker

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For over 431 million years the rate of the beating heart has been coupled with breathing. The earliest cartilaginous fish showed this. Preservation of respiratory heart rate coupling (rHRV) is found throughout the animal kingdom and is an index of health and physical fitness. In contrast, the loss of rHRV is associated with cardiovascular disease and a prognostic indicator of sudden cardiac death. The questions we asked are why do cardiac pacemakers pace metronomically when Nature paces with variability, and does this matter?

All animal and human studies were ethically approved by university and national regulatory bodies, respectively. We induced heart failure with reduced ejection fraction in sheep (ewes) by injection of microbeads into the coronary artery to reduce ejection fraction to ~40%. Sheep were paced either metronomically or with a novel pacemaker to reinstate rHRV for four weeks. Cardiac output and coronary blood flow were measured chronically. Sheep were exercised on a variable incline treadmill. Heart tissue was taken for post-hoc analyses. A first-in-human safety and feasibility trial was conducted in patients after coronary artery bypass graft surgery where rHRV was induced via temporary transcutaneous pacing leads for up to 5 days.

Cardiac output increased by ~24% and there was a reduction in dis-ordered breathing in the rHRV paced sheep compared to those paced metronomically. This was accompanied by improvements in exercise haemodynamics including cardiac output, coronary blood flow and heart rate recovery time to control levels post-exercise. The improvement in cardiac output persisted in a separate group of heart failure animals treated with medications suggesting a novel mechanism of repair. Cardiac tissue studies indicated that rHRV pacing repaired the expression of t tubules and ryanodine receptors and increased their co-localisation. Proteomics revealed increased expression of mitochondrial proteins associated with energy production and efficiency. Electron microscopy indicated repair of mitochondrial cristae with rHRV pacing; this was not seen with metronomic pacing. rHRV pacing in heart failure patients proved to be feasible and safe without adverse effects.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.32 Stellate Ganglion Modulation To Control Autonomic Transmitter Release

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The autonomic nervous system governs cardiac function through a finely balanced interplay of sympathetic and parasympathetic activity. Following myocardial infarction (MI), chronic sympathetic hyperactivation destabilizes this balance, increases arrhythmia formation, and progresses cardiac dysfunction. Current treatments such as pharmaceuticals, surgical sympathectomies, and ablations, are either systemic, irreversible, or non-titratable, underscoring the need for targeted, adaptive interventions. Alternatively, electrical sympathetic nerve block is a treatment that can be applied instantly, is rapidly reversible, and can be titrated to customizable dosage. Norepinephrine (NE) is the primary neurotransmitter released from postganglionic sympathetic efferent nerves and increases cardiac mechanical and electrical function. NE levels can be measured in real-time using fast scanning cyclic voltammetry (FSCV). A closed-loop controller was used to detect changes in NE levels and respond with graded electrical nerve block of the paravertebral chain. Direct current (DC) electrical nerve block was provided using a carbon separated interface nerve electrode (CSINE). A fuzzy logic controller (FLC) was designed to titrate the level of nerve block to maintain the NE release at a pre-defined threshold (the “setpoint”). Programmed ventricular pacing was used as a stressor to elicit NE release and the controller was used to attenuate sympathetic drive to clamp the NE output at the setpoint. NE was successfully maintained at the selected thresholds for the duration of the pacing and the NE levels resumed the initial values after the intervention was completed. This treatment was tested in both normal and chronic myocardial infarction (MI) porcine models. The FLC successfully controlled NE levels in both the normal and disease model demonstrating the ability of closed-loop control to respond to the progression of disease.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.33 Modulation Of Renal Interoception To Treat Cardiometabolic Diseases: What Is The Kidney Whispering To, Or Shouting At, The Brain?

John Osborn (1)* - *Lucy Vulchanova (2)* - *Louise Evans (3)* - *Christopher Banek (1)* - *Mariana Ruiz Lauar (1)* - *Alex Dayton (4)* - *Brianna Dailey-krempel (2)

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The kidneys are regulated by sympathetic (efferent) control of the renal vasculature, renin release, and tubular transport. The kidneys are also innervated by sensory neurons that relay information to the central nervous system. This sensory (afferent) input modulates not only neurohormonal systems, but also interoceptive circuits to maintain homeostasis. Many of the beneficial effects of catheter-based renal denervation (CBRDN) for treatment of hypertension may be due to ablation of afferent, rather than efferent, renal nerves. This suggests that targeted modulation of afferent renal neurons could be beneficial for treatment of disease. Here we review our collective research on the role of renal interoception in pathophysiology.

We have shown that afferent renal nerve activity (ARNA) is 2.5x higher in rodent models of mineralocorticoid-salt hypertension compared to normotensive controls. In this model, afferent renal denervation (ARDN) is as effective at decreasing blood pressure (BP) and global sympathetic nerve activity (gSNA) as total renal denervation (TRDN). Using two bottle preference tests, we have demonstrated that ARDN reduces saline, but not water intake, in this model. These studies suggest that the efficacy of CBRDN may be explained, in part, by reducing salt intake. Blockade and knockout of the inflammatory cytokine interleukin 1 receptor (IL-1R) has identical effects as ARDN on BP. The combination of ARDN and IL-1R blockade is not additive, suggesting a relationship between IL-1R and afferent renal nerves in mineralocorticoid-salt hypertension. Similarly, in the 2-kidney 1-clip model of renovascular hypertension, ARNA is also elevated, and ARDN is as effective as TRDN in decreasing BP, gSNA, water intake, and vasopressin levels. Preclinical studies in rodents suggest that ARDN may be an effective treatment for polycystic kidney disease by reducing cyst formation. Although the mechanism is currently under investigation, it appears to be linked to the regulation of vasopressin signaling.

Taken together these findings indicate that modulating renal interoceptive pathways using novel bioelectronic approaches is a potentially powerful pathway for clinical innovation. Current research spans from single cell transcriptomics of renal specific sensory neurons to identify their sensory modalities, to the development of an implantable renal neuromodulatory device designed to treat hypertension.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.34 Selective vagal neuromodulation for cardioprotection: mechanistic and preclinical foundations

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Increased efferent vagal drive protects the ischaemic and failing heart, yet large clinical trials of cervical vagus nerve stimulation (VNS) in heart failure have not met their primary endpoints. A probable reason is that conventional electrical VNS is non-selective, co-activating afferent, efferent and off-target fibres and thereby diluting the intended cardiac effect. This talk outlines a translational framework, developed over more than a decade across several laboratories, that identifies the cardioprotective vagal output and establishes the basis for engaging it selectively.

The cardioprotective output was first isolated using cell-specific optogenetics. Vagal pre-ganglionic neurones of the dorsal motor nucleus of the vagus (DVMN) were transduced with a lentiviral vector to express the light-sensitive channel ChIEF. Optogenetic activation of these neurones reduced infarct size in a rat model of acute ischaemia/reperfusion injury, mimicking remote ischaemic preconditioning, while their silencing abolished it; the effect was muscarinic receptor-dependent (PMID:22739118). Applied chronically in rat post-infarction heart failure, the same approach preserved left ventricular ejection fraction and exercise capacity, without reducing infarct size (PMID:32875170), indicating that cardioprotection is conveyed specifically by DVMN efferents.

Feasibility of this approach in a large, multi-fascicular nerve was shown in sheep: after lentiviral ChIEF transduction of DVMN neurones, light delivered to the cervical vagus evoked selective efferent action potentials remote from the brainstem (PMID:33217609), providing electrophysiological proof of concept for selective efferent activation at a clinically relevant site.

To map fascicular organisation directly, electrical impedance tomography with ring-electrode arrays for spatially selective VNS (sVNS) was validated against micro-computed tomography, revealing an organised topography in the porcine cervical vagus (PMID:37205051). Anatomical tracing in the human cervical vagus identified cardiac, pulmonary and laryngeal fascicles that retained partial organotopic organisation near their branch points, though fascicles merged toward the cervical level (PMID:41788551). In pigs, sVNS then selectively modulated cardiac function in vivo, with heart-rate responses identifying cardiac efferent fascicles spatially separated from cardiac afferents (PMID:39183636). Whether these heart-rate-defining cardiac efferents coincide with the cardioprotective DVMN efferent pathway is unresolved and central to translation.

Selective engagement of the DVMN efferent pathway is therefore the key challenge for translating vagal cardioprotection into a clinical device.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.35 Spatially Selective Vagus Nerve Stimulation Reveals Functional Organisation Of Human Cardiac Vagal Fibres

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Traditional cervical vagus nerve stimulation (VNS) activates the entire nerve trunk, often causing off-target effects and/or nullifying desired cardiac effects through concurrent activation of afferent and efferent fibres. This limits its clinical utility for cardiac applications, specifically in heart failure, where targeted parasympathetic activation of cardiac efferents is required to counteract maladaptive tissue remodelling following myocardial infarction. Spatially selective VNS (sVNS) provides an opportunity to address this by selectively activating cardiac-specific vagal efferent fibres. This could enhance therapeutic precision while avoiding concurrent activation, adverse effects and excessive titration. Previous preclinical work demonstrated independent modulation of cardiac, pulmonary, and laryngeal responses using sVNS1. More recently, segregation of cardiac afferent and efferent fibres was demonstrated in pigs2. Here, we aimed to characterise this organisation in humans.

A multi-electrode sVNS cuff (2 rings x 14 electrodes) was implanted at the mid-cervical level of the exposed left VN in consenting epilepsy patients already undergoing surgery for, but before implantation of, the FDA approved device (NCT05664854/REC22/LO/0463). Surface EMG electrodes were placed to capture laryngeal activity. Full-nerve stimulation was applied at incremental current (0.5-2mA, 15s) to identify an individualised current threshold producing a 3–10% heart rate (HR) decrease. The optimised current was delivered sequentially through each electrode pair while recording HR, respiratory rate, and EMG responses.

Preliminary in vivo results in humans (n=9) showed variable HR responses (~5% tachycardia or bradycardia) with full VNS. During sVNS, reproducible, selective bradycardia of 6.3%±2SE and tachycardia of 3.5%±1SE were achieved. The average angular separation between the electrode pairs eliciting the most prominent bradycardia and tachycardia responses was 227º±13SE (p=5.7x10^-8), indicative of significant spatial segregation and selective activation.

Distinct separation between cardiac afferent and efferent regions was observed, consistent with findings in porcine models and supporting conserved cardio-vagal organisation. The ability to selectively stimulate cardiac efferents without reflex afferent activation or laryngeal side effects demonstrates the feasibility of spatially targeted cardiac neuromodulation in humans. This study provides the first functional evidence of selective cardiac efferent activation within the human VN. These findings support the translational potential of sVNS to achieve cardiac-specific neuromodulation for parasympathetic restoration in heart failure.

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.24 Effects Of 4-week Transcutaneous Vagus Nerve Stimulation On Orthostatic Tachycardia, Autonomic Symptom Burden, And Inflammation In Long-COVID POTS

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Background: Postural orthostatic tachycardia syndrome (POTS) is an increasingly recognized autonomic sequela of Long COVID (LCPOTS). We previously demonstrated reduced parasympathetic nervous system (PNS) activity in this population; however, whether restoring PNS function improves clinical outcomes and inflammation remains unknown. The aim of this study was to determine the effects of 4-week active transcutaneous vagus nerve stimulation (tVNS) compared with sham on orthostatic tachycardia, symptom burden, and inflammatory cytokines in 30 LCPOTS patients. We hypothesized that tVNS would reduce orthostatic tachycardia, improve autonomic symptom burden, and decrease inflammatory biomarkers compared with sham stimulation.

Methods: Subjects were randomized 1:1 to active tVNS or sham stimulation for 28 days. Active stimulation was delivered using a TENS 7000 device with ear-clip electrodes placed at the concha (tVNS) versus earlobe (sham) twice a day for one hour. Continuous ECG and beat-to-beat blood pressure monitoring were collected during 10 min of supine baseline and 30 min of 75-degree head-up tilt (HUT). Autonomic symptoms were measured using the Vanderbilt Orthostatic Symptom (VOSS) during HUT, and the Composite Autonomic Symptom Score-31 (COMPASS-31). Parasympathetic activity was assessed through spectral analysis of heart rate variability, with high-frequency R-R interval variability (HF-RRI) used as an index of cardiovagal modulation. Inflammatory biomarkers, including IL-6, IL-1β, TNF-α, and IL-10, were measured before and after treatment using multiplex immunoassays.

Results: Forty-eight patients with LCPOTS were enrolled, and thirty were randomized 1:1 to active tVNS or sham stimulation. Participants had a mean age of 33.5 ± 9.6 years, were 90% females, had a mean body mass index 25.4±4 kg/m2, and mean symptom duration of 34 ±15 months. Final analyses are ongoing and are expected to be completed in July 2026. Primary analyses will evaluate the effects of tVNS on orthostatic heart rate responses during standing and head-up tilt testing, as well as acute and chronic orthostatic symptom burden measured by VOSS and COMPASS-31, cardiovagal modulation measured by HF-RRI, and circulating inflammatory cytokines.

Conclusion: This randomized, double-blind, sham-controlled trial will provide prospective evidence on the therapeutic potential of vagal neuromodulation to improve autonomic function, alleviate symptom burden, and reduce inflammation in patients with Long-COVID POTS.

10TH Symposium - PRECISELY WHAT IS TORPOR? CAN WE SYNTHESISE IT?

TOPIC 08: Autonomic control of metabolism and energy homeostasis

S.36 Autonomic Changes During Natural Torpor In The Mouse

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Daily torpor in the mouse requires two permissive conditions: a cool environment and a caloric deficit. Under these conditions, mice can dramatically lower metabolic rate, inducing a subsequent fall in body temperature, producing substantial energetic savings to improve survival. Both entry into torpor and subsequent arousal involve coordinated adjustments of the autonomic nervous system that regulate heat production, heat conservation, and cardiovascular function. In a cool environment, sympathetic activation of the tail vasculature promotes vasoconstriction minimizing heat loss. Tail blood flow remains minimal throughout the bout of torpor. White adipose tissue is likewise under sympathetic control. Its activation lowers circulating leptin, a hormone critical for gating torpor, and stimulates lipolysis, providing circulating fatty acids that serve as an important fuel source during torpor. Before body temperature declines, pronounced parasympathetic influence on the heart produces marked sinus arrhythmia and bradycardia, reducing cardiac work and contributing to overall metabolic savings. Conversely, emergence from torpor is initiated by sympathetic activation of brown adipose tissue, triggering non-shivering thermogenesis to drive the rise in metabolic rate and subsequently body temperature. Simultaneously during arousal, sympathetic activation of the heart, coupled with parasympathetic withdrawal, elevates the heart rate as the metabolic rate returns to euthermic levels. Thus, the autonomic nervous system orchestrates a series of tissue-specific responses that conserve energy during torpor and restore homeostasis during arousal. Whether synthetic torpor captures all of these aspects of autonomic control, and the appropriate timing of autonomic changes, remains to be determined.

TOPIC 08: Autonomic control of metabolism and energy homeostasis

S.37 Engineering Hibernation: Exploring Synthetic Torpor Induction Methods And Future Perspectives

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Synthetic torpor (ST) is attracting increasing interest as a strategy to reproduce the hypometabolic and hypothermic state of natural hibernation in non-hibernating species. Beyond its biological relevance, ST holds considerable translational potential for applications ranging from critical care medicine and organ preservation to long-duration spaceflight. However, despite remarkable progress over the last decade, no single strategy has emerged as the optimal approach for inducing this state in non-hibernators.

This presentation will provide an overview of the principal methods currently used to induce ST and discuss their advantages, limitations and potential for translation. Particular attention will be given to approaches targeting central thermoregulatory circuits, including pharmacological, physical and neuromodulatory strategies, highlighting how they differ in terms of invasiveness, specificity and reversibility.

Recent advances in the understanding of the neural circuits controlling thermoregulation have shifted the focus from broad inhibition of neuronal activity toward selective manipulation of defined cell populations. This transition is opening new possibilities for developing more precise and reproducible methods to induce ST while improving our understanding of the neural mechanisms underlying torpor and hibernation.

Finally, future perspectives will be discussed, with particular emphasis on circuit-based neuromodulation, cell-type-specific approaches and emerging technologies that may help bridge the gap between proof-of-concept studies and clinically relevant applications. By integrating current knowledge with recent technological advances, this presentation aims to provide a framework for understanding how ST induction is evolving from empirical manipulation toward a more rational engineering of hibernation.

TOPIC 11: Emerging concepts and novel perspectives in autonomic neuroscience

S.38 Brain Circuits And Central Mechanisms Enabling Survival Under Extreme Conditions

Amelia Douglass (1) - Nicole Lynch (2) - Matias Andina (3) - Oscar Ramirez-plascencia (2) - Hakan Kucukdereli (1) - David Melville (2) - Luis Costa (2) - Yuellin Yang (2) - Chenxi Qiu (2) - Alexander Banks (2) - Sinisa Hrvatin (3) - Clifford Saper (2) - Bradford Lowell (2) - Natalia Machado (2)

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Homeothermic animals, including humans, regulate their body temperature (Tb) at a nearly constant level to maintain physiological functions and survival. For example, in response to changes in ambient temperature (Ta), these animals display both behavioral (e.g., seeking warmer or colder environments) and physiological adjustments, such as heat production or heat dissipation, required to maintain the body temperature around 37 °C (normothermia). These responses are regulated by the central nervous system (CNS), which, despite its fine control over Tb and energy expenditure (EE), can produce increases in metabolic rate and Tb during immunological insults, a phenomenon we call fever. On the flip side, to survive periods of negative energy balance, brain-mediated mechanisms lower Tb and EE, supporting energy conservation and physiological adaptation to these adverse conditions. Mice, for example, show daily torpor that may last several hours to bridge the lack of energy availability in a cold environment. While our recent studies identified a population of neurons in the median preoptic nucleus (MnPO) necessary for fasting-induced torpor regulation, the specific brain circuits that trigger energy conservation in response to food restriction are unknown.

We investigated the central pathways by which the animal's energy state is conveyed to preoptic neurons. We first found that the activity of neurons in the arcuate nucleus expressing Agouti-Related Peptide (ARCAgRP) are required for the generation of fasting-induced torpor. Then, we showed that torpor-active ARCAgRP neurons innervate the preoptic area of the hypothalamus, including the MnPO.

Using optogenetic methods, we also found that activating the ARCAgRP→MnPO pathway induces key features of torpor: decreased body temperature (-2.28 ± 0.23 oC), bradycardia (367.9 ± 8.3 bpm), reduction of energy expenditure (-0.08 ± 0.02 Kcal/hr), and suppression of brown adipose tissue thermogenesis (-2.36 ± 0.34 oC). Remarkably, we also show that inhibition of the ARCAgRP→MnPO brain circuit entirely prevents fasting-induced torpor. Furthermore, we identified that both NPY and GABA are neuromodulators used by ARCAgRP neurons to enable hypothermic responses during starvation.

Our studies provide a detailed view of a hypothalamic pathway enabling energy conservation, a survival mechanism in conditions of low energy availability.

TOPIC 11: Emerging concepts and novel perspectives in autonomic neuroscience

S.39 Synthetic Torpor: Clone Or Counterfeit

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Torpor is a naturally occurring phenomenon characterised by dramatic reductions in metabolism, body temperature, and heart rate from homeostatic norms, co-ordinated by neurons in the pre-optic area of the hypothalamus (POA). Recent studies (1, 2) have used the TRAP system to chemogenetically-activate POA neurons and recapitulate the body temperature drop observed in natural, fasting-induced torpor. Activating POA neurons also triggers tail vasodilatation (3), which we have not observed in fasting-induced torpor. We aimed to assess whether this vasodilatation reflects an engagement of warm-sensing neurons in synthetic torpor, thus weakening it as a true replication of fasting-induced torpor.

To test autonomic thermoregulation, we used thermal imaging to record tail temperature before and after injecting torpor-TRAPed Fos2A-iCreER (TRAP2) mice (n=4) with 2mg/kg CNO i.p. and compared this with tail temperature in fasting-induced torpor (n = 6). To assess behavioural thermoregulation, we used a custom-built thermal gradient. Torpor-TRAPed (n = 8), or C57BL/6J control mice (n=6) were injected with 2mg/kg CNO i.p. and then placed in the centre of the gradient with their position tracked for 1 hour post-injection.

In the torpor-TRAPed group, we observed a significant increase in tail temperature from baseline of over 30% for 30 minutes following CNO injection. Meanwhile, tail temperature in the fasted group showed no significant difference for the 30-minute period pre- and post- their body temperature starting to drop. The torpor-TRAP mice also expressed a preference for the warm end of the thermal gradient, adopting an elongated posture between 32.5°C and 37.5°C. This position preference differed significantly from the control mice from 15 minutes post-injection. With the ramp turned off, torpor-TRAP mice expressed a hunched posture and showed no difference in position preference to controls.

The position and postural response strongly suggests that the torpor-TRAPed mice do not feel warm as they enter synthetic torpor, and their behaviour reflects the response of fasted mice on a thermal gradient (4). This provides evidence that synthetic torpor is an accurate model for natural torpor. However, we are yet to determine whether the vasodilatation is a side-effect of our TRAPing procedure or a feature unique to synthetic torpor.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.25 Synthetic Torpor In The Rat Protects The Heart From Ischemia-reperfusion Injury

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Introduction: Torpor is a remarkable, reversible hypometabolic state characterised by dramatic reductions in body temperature, heart rate, and oxygen consumption. Cycling from normal physiology to torpor and back produces enormous changes in cardiac output and tissue perfusion, and yet the animal tolerates this with no detectable injury. Indeed, animals that naturally enter torpor are highly tolerant of ischemia-reperfusion injury. It is currently unknown, however, whether a torpor-like state is protective in species that do not naturally enter torpor.

Methods: Using viral vector-mediated chemogenetic activation of the medial preoptic area (MPA) within the hypothalamus, we induced synthetic torpor in the rat, a species that does not naturally enter torpor. We then tested ex vivo ischaemia-reperfusion tolerance in hearts taken from animals in synthetic torpor compared to controls. Finally, we performed phosphoproteomic analysis in hearts to identify up- and down-regulated signalling pathways.

Results: Chemogenetic activation of CAMKIIα expressing neurons within the MPA using intraperitoneal Clozapine-N-oxide (2 mg/kg) recapitulates three key features of torpor: hypothermia, bradycardia, and reduced oxygen consumption. We demonstrate this synthetic torpor state is cardioprotective in an ex vivo ischemia-reperfusion injury model, resulting in a 40% reduction in cardiac infarct size compared to controls. This torpor-induced cardioprotection of the isolated heart is not dependent on prior hypothermia in vivo. Phosphoproteomic analysis of cardiac tissue 90 minutes post synthetic torpor indicates that the cardioprotective effect of synthetic torpor is mediated by parallel activation of cell survival and stress tolerance pathways, alongside inhibition of cell death pathways.

Conclusion: These findings suggest that conserved mechanisms exist in species that do not naturally enter torpor, and that this state is cardioprotective. This supports the hypothesis that mimicking torpor could be protective in human clinical settings.

TOPIC 04. Neuroimmune communication and neural control of immune responses

O.26 Whole-brain Mapping Of Neuronal Populations Engaged During LPS-induced Hypothermia

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Introduction: Lipopolysaccharide (LPS) is a mimic of Gram-negative bacterial infection. LPS can drive either a hypothermic or a hyperthermic (febrile) response, whose prognostic significance remains debated. Which predominates depends on dose - higher doses favouring hypothermia - but also on the metabolic state of the organism. LPS-induced hypothermia is thus not just a passive failure of thermogenesis but a regulated state, integrating immune with metabolic demands. Torpor is another form of regulated hypothermia, used by many species, including mice, as a survival strategy, suggesting the possible existence of overlapping neuronal circuits driving hypothermia as a defensive strategy. The neuronal populations governing torpor entrance have been mapped and described across several brain regions. No comparable characterisation exists for LPS-induced hypothermia.

Methods: We used TRAP2:Ai14 mice, in which Fos-driven, tamoxifen-dependent CreERT2 activity recombines the Cre-dependent Ai14 reporter, permanently labelling neurons activated within ~3hours from tamoxifen administration with tdTOMATO. Mice were implanted with an intraperitoneal telemetry probe (locomotor activity, core body temperature and heart rate) and housed at 22±1°C. Animals received 4-hydroxytamoxifen (25mg/kg, i.p.) concomitantly with LPS 5mg/kg, LPS 3mg/kg or saline (i.p.). After 72h, animals were culled by anaesthetic overdose, transcardially perfused, and the brains collected. Serial coronal brain sections were DAPI-counterstained and imaged on an Olympus VS200 slide scanner, then registered to the Allen Mouse Brain Atlas. tdTOMATO-positive cells were quantified as a percentage per region and compared across groups.

Results: LPS induced hypothermia, at both 3mg/kg (nadir temperature: saline 34.86±0.36°C vs. LPS 24.28±2.54°C; Sidak p=0.031) and 5mg/kg (nadir temperature: saline 34.86±0.36°C vs. LPS 24.16±2.20°C; Sidak p=0.0194).

Preliminary mapping indicates that LPS engages a defined, neuronal network, comprising brainstem structures implicated in autonomic and immune-to-brain signalling - such as the nucleus of the solitary tract (NTS) and the area postrema (AP) - and hypothalamic nuclei, including the ventrolateral preoptic (VLPO) and the paraventricular hypothalamic nucleus (PVH). Comparative analysis is ongoing.

Conclusions: These preliminary data suggest that the thermoregulatory adaptations characterising LPS response are, at least partially, centrally co-ordinated. Hypothalamic recruitment is, moreover, consistent with an overlap with torpor circuitry, supporting the proposal of a shared neural substrate producing regulated, defensive hypothermia.

11TH Symposium - CARDIAC INNERVATION PATTERNS GOVERNING CARDIOVASCULAR FUNCTION IN HEALTH AND DISEASE

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.40 Innervation Of The Human Heart And Changes Associated With Cardiomyopathy

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Introduction: Progression of cardiac disease involves a dynamic interaction between adverse remodeling of the cardiac substrate and the cardiac nervous system that regulates it. Yet, detailed regional innervation of the normal and pathologic human heart has not been characterized at the tissue level. We hypothesized that innervation patterns in cardiomyopathic hearts are significantly different from those in normal hearts.

Methods: We used immunohistochemistry (IHC) to label noradrenergic (tyrosine hydroxylase, TH) and cholinergic (vesicular ACh transporter, VAChT) nerves in two donor human hearts rejected for transplant and three hearts from patients with heart failure due to non-ischemic (NICM) or ischemic cardiomyopathy (ICM). Hearts were fixed in cold 4% paraformaldehyde, IHC was performed on 30 um sections, and nerve densities quantified.

Results: TH and VAChT nerves were identified in nine atrial regions at similar densities (TH range: 1.8% area at sinoatrial [SA] node to 0.42% for mitral region; VAChT range: 2.99% at SA node to 0.42% for mitral region). Innervation was evaluated in four right ventricular (RV) and 11 left ventricular (LV) regions.

TH-positive nerves were abundant at all levels of ventricular myocardium from base (0.45%) to apex (0.40%). VAChT-positive nerves were less abundant in ventricles than atria, less abundant than TH-positive nerves in ventricles, and scarce at the apex. While TH-positive and VAChT-positive nerves were maintained in atrial regions from NICM hearts, TH nerve density was doubled on the right compared to the left. TH nerve density was also increased in several regions of RV and LV myocardium of NICM hearts compared to normal donor hearts. VAChT nerves were maintained in RV areas of both NICM hearts and in one LV. Fibrosis and loss of VAChT were evident in the other NICM heart. The ICM heart showed heterogeneous TH innervation and depletion of

VAChT nerves. Nerves were also reduced in the left atrium, but the right atrium was hyperinnervated (TH and VAChT).

Conclusions: Balanced TH and VAChT innervation occurs in normal atria, basal RV/LV, and LV subendocardium. In NICM and ICM, this pattern is altered leading to heterogeneous enrichment in sympathetic innervation.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.41 Cardiac Sympathetic Neurons: Victims And Culprits In Arrhythmogenic Cardiomyopathy (ACM)

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Arrhythmogenic cardiomyopathy (ACM) is an inherited disorder characterized by ventricular arrhythmias, progressive myocardial remodeling and sudden cardiac death, particularly in young individuals and athletes. Although pathogenic variants in desmosomal genes are central to disease pathogenesis, the mechanisms linking genetic defects to arrhythmogenesis and structural progression remain incompletely understood.

We hypothesized that sympathetic neurons contribute directly to ACM progression. Using mouse models carrying pathogenic variants in desmoglein-2 (DSG2) and desmoplakin (DSP), together with human ACM samples, we investigated sympathetic neuronal morphology, cardiac innervation and the consequences of sympathetic denervation.

Sympathetic neurons expressed desmosomal proteins, including DSG2. In Dsg2 mutant mice, sympathetic neurons showed abnormal morphology, with altered axonal thickness, branching and varicosity distribution. These abnormalities were already detectable before overt myocardial remodeling and were accompanied by marked changes in cardiac sympathetic innervation. In particular, mutant hearts displayed heterogeneous sympathetic fiber distribution and subepicardial hyperinnervation, a region in which myocardial remodeling typically begins. Comparable alterations were observed in human ACM samples and in a DSP cardiomyopathy model, although with genotype-specific neuronal features.

Preliminary functional studies further suggest altered calcium dynamics and transcriptional pathways related to neuronal activation and neurotransmission in mutant sympathetic neurons. Importantly, chemical cardiac sympathetic denervation in Dsg2 mutant mice preserved contractile function and reduced fibrotic remodeling, supporting a causal contribution of sympathetic input to disease progression.

These findings support a neuro-cardiac model of ACM in which sympathetic neurons are both affected by desmosomal mutations and active contributors to myocardial dysfunction and remodeling. Targeting sympathetic signaling, potentially beyond classical adrenergic blockade, may therefore represent a promising therapeutic avenue in ACM.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.42 Investigating End-organ Regulation Through Direct Cardiac Autonomic Nerve Recordings

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While plasma biomarkers and heart rate variability are common surrogates for autonomic activity, they lack the temporal and spatial resolution needed to determine what the heart receives in real-time. Sympathetic transduction is the study of how impulses from the sympathetic nervous system affect end-organ function. While this relationship is well-established for resting muscle sympathetic nerve activity (MSNA), direct cardiac sympathetic transduction remains poorly understood, and the parallel vagal transduction of cardiac end-organ responses has not yet been assessed. We aimed to investigate how directly recorded resting cardiac sympathetic nerve activity (CSNA) and cardiac vagal nerve activity (CVNA) dynamically regulate cardiac function. Adult sheep were instrumented to achieve direct, intra-thoracic, recordings of CSNA or CVNA, depending on group. Simultaneous measurements of beat-to beat, heart rate, coronary blood flow, coronary vascular conductance, cardiac output, and mean arterial pressure were acquired. All experiments were performed at least one week after instrumentation surgery in conscious animals at rest. Modified signal-transduction methods were applied to measure how spontaneous bursts of neural activity trigger immediate end-organ responses. Signal transduction analysis revealed that each spontaneous CSNA burst triggered a significant elevation in heart rate, immediately followed by a compensatory increase in coronary blood flow. Crucially, these tachycardic changes were graded according to the precise size and pattern of the preceding CSNA bursts, and were significantly attenuated following propranolol. CVNA exhibits distinct burst profiles; spontaneous CVNA bursts triggered rapid, transient decreases in heart rate that was dependent on the specific burst type, with burst incidence correlating with blood pressure. Establishing end-organ effects from directly recorded cardiac autonomic nerve activity will help establish a high-resolution framework for understanding autonomic control of the heart in conscious large mammals.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.43 - Heterogeneous Cardiac Sympathetic Innervation Gradients Promote Arrhythmogenesis In Murine Dilated Cardiomyopathy

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Sympathetic activation contributes to ventricular arrhythmias (VAs) in heart failure, yet patients with reduced cardiac sympathetic innervation are paradoxically at greater arrhythmic risk. We hypothesized that this association reflects uneven sympathetic denervation in failing hearts. Using murine models of dilated cardiomyopathy (DCM), [11C]meta-Hydroxyephedrine PET imaging revealed widespread ventricular hypoinnervation with pronounced transmural gradients, characterized by severe loss of endocardial sympathetic fibers. The magnitude of these gradients correlated with VA burden and was also observed in human DCM ventricular tissue. Computational 1D, 2D, and 3D models of normal and failing human hearts demonstrated that increasing innervation heterogeneity promotes arrhythmogenesis, particularly when combined with DCM-related electrical remodeling. These findings identify transmural sympathetic denervation gradients as a key substrate for arrhythmia generation in DCM and suggest that restoring more uniform cardiac innervation may reduce VA risk.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.27 Spinal Afferent Innervation From The Left Dorsal Root Ganglia In Flat-mounts Of Whole Ventricles Of Rats: Anterograde Tracing

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Spinal afferents relay sensory information and regulate cardioprotective reflexes. These afferent signals go to cell bodies in the dorsal root ganglia (DRG) and ultimately to the central nervous system. However, the morphology and distribution of spinal afferent terminals in the heart have not been well delineated. This is partly due to challenges, including limited surgical access to the upper thoracic DRGs, tissue thickness, and tracer options. In this study, we injected tracer dextran biotin (DB) into the left DRG (C8-T3) of male Sprague-Dawley rats (3-5 months). After 16 days, the animals were sacrificed, and the left and right ventricles were separated from the rest of the heart. Next, these samples were stained with diaminobenzidine and mounted for visualization under brightfield microscopy. DB-labeled axons were identified and digitally traced using the Neurolucida system. Our findings showed that spinal afferent neurons of the left DRG C8-T3 project individual axons that enter the ventricles from the bases of the heart. These axons are distributed across various regions within both the left and right ventricles, with a higher prevalence observed in the left ventricle. Furthermore, these spinal afferent axons predominantly target the posterior regions of both the left and right ventricles. While these axons are present in the epicardial and myocardial layers, DB-labeled axons were not identified in the endocardial layer. Within the epicardial and myocardial layers, spinal afferents form both simple and complex terminal arborizations and make close contact with cardiac muscle. This investigation marks the first anterograde characterization of spinal afferent axon terminal distribution and morphology in flat-mount preparations of whole ventricles. Supported by NIH 1R01HL173868-01A1 and 1 U01 NS113867-01.

TOPIC 08. Autonomic control of metabolism and energy homeostasis

O.28 Organ-selective Sympathetic Preganglionic Neurons Across Metabolic Organs Reveal Segregated Circuits And Distinct Molecular Signatures

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The sympathetic nervous system (SNS) maintains metabolic homeostasis by coordinating signals across various peripheral organs. Sympathetic preganglionic neurons (SPNs), located in the intermediolateral column of the thoracolumbar spinal cord, serve as the primary integrative hub for these signals. While anatomical distributions of SPNs have been suggested, the molecular markers defining their organ-selective functional identities remain largely undeciphered.

In this study, we employed pseudorabies virus (PRV) retrograde tracing combined with tissue clearing to map the 3D neural circuitry of major metabolic organs. Retrograde labeling from the interscapular brown adipose tissue (iBAT) and myocardium revealed a distinct subset of co-localized SPNs. This shared circuitry provides a neuroanatomical basis for the cardioexcitatory side effects associated with thermogenic anti-obesity therapies. In contrast, tracing from subcutaneous (iWAT) and visceral (eWAT) white adipose tissue demonstrated highly segregated SPN populations with minimal overlap and strong laterality. Spinal cord clearing and 3D reconstruction further visualized the discrete, non-overlapping spatial organization of these organ-specific SPN clusters within the spinal architecture.

The predominance of organ-selective SPNs, particularly between different adipose dePOTS, underscores the necessity of defining their unique molecular signatures. To address this, we are currently utilizing spatial transcriptomics (Visium HD) to identify organ-selective molecular markers within the spinal cord. By deciphering these molecular identities, this research aims to provide a framework for developing precise, organ-targeted metabolic interventions that minimize off-target cardiovascular effects.

12TH Symposium - AUTONOMIC DYSFUNCTION IN MULTIPLE SCLEROSIS: FROM MECHANISMS TO CLINICAL IMPLICATIONS

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.44 How do the autonomic and immune systems communicate in multiple sclerosis?

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Introduction: Autonomic nervous system (ANS) dysfunction is increasingly recognized as an extraintestinal manifestation of inflammatory bowel disease (IBD). Although altered heart rate variability (HRV) has been associated with disease activity in adults, the relationship between autonomic dysfunction and short-term inflammatory activity in pediatric IBD remains poorly understood. We investigated whether autonomic symptoms, formal autonomic function testing, and HRV parameters could serve as biomarkers of disease activity in children with IBD.

Methods: In this prospective observational study, 33 children and adolescents with IBD underwent comprehensive autonomic evaluation, including autonomic symptom assessment using the Composite Autonomic Symptom Score-31 (COMPASS-31), standardized autonomic reflex testing with Composite Autonomic Scoring Scale (CASS) calculation, and ECG-based HRV analysis during supine rest and head-up tilt testing. Disease activity was defined as fecal calprotectin >150 µg/g within 30 days following autonomic assessment. Univariable and multivariable logistic regression analyses were performed to identify autonomic predictors of disease activity.

Results: Twelve children (36%) had active disease. Children with active disease had higher COMPASS-31 scores [11.33 (IQR 32.05) vs. 3.35 (IQR 3.90), p=0.045] and a higher prevalence of symptomatic dysautonomia (57.1% vs. 16.7%, p=0.043). During head-up tilt testing, active disease was associated with lower high-frequency power (HFt; p=0.011), lower normalized high-frequency power ($HFnu_t$; p=0.005), and higher LF/HF ratio (p=0.005), indicating reduced parasympathetic modulation and relative sympathetic predominance. No significant differences were observed in resting HRV parameters or CASS scores. In univariable analysis, $HFnu_t$, LF/HF_t, female sex, and COMPASS-31 >7.913 were associated with disease activity. In multivariable logistic regression, $HFnu_t$ remained the only independent predictor of disease activity (OR 0.85, 95% CI 0.72–1.00, p=0.048).

Conclusion: Children with active IBD exhibit increased autonomic symptom burden and impaired parasympathetic regulation during orthostatic stress. Among comprehensive autonomic assessments, HFnu during head-up tilt emerged as the strongest independent predictor of short-term inflammatory activity, suggesting that stress-induced autonomic responses may serve as non-invasive biomarkers of disease activity in pediatric IBD.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.45 Central Autonomic Network Disturbance In Multiple Sclerosis: Implications For The Clinic And Research

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Introduction. Autonomic dysfunction is common in multiple sclerosis (MS), may occur early in the disease course, and remains insufficiently captured by conventional disability measures. Autonomic symptoms may involve cardiovascular, secretomotor, gastrointestinal, bladder, and pupillomotor domains. Fatigue, one of the most frequent and disabling symptoms in MS, has been associated with autonomic symptom burden, although the mechanisms linking dysautonomia and fatigue remain incompletely understood. Since standard autonomic testing mainly reflects peripheral autonomic output, evidence on central autonomic pathophysiology in MS remains limited. Advanced magnetic resonance imaging (MRI) techniques provide an opportunity to investigate central autonomic regulation in vivo.

Methods. This lecture will summarize recent MRI evidence on central autonomic network (CAN) dysfunction in MS. Studies from our group specifically designed to investigate CAN alterations in MS will be presented and discussed. To better characterize the mechanisms related to CAN dysfunction, we investigated resting-state (RS) functional connectivity (FC) and effective connectivity (EC) alterations of the CAN in patients with MS using seed-based analyses and spectral dynamic causal modelling. The relationship between CAN connectivity abnormalities and fatigue severity was also assessed. Moreover, the ability of aerobic training (AT) to modulate CAN connectivity was explored.

Results. CAN dysregulation is present in MS, with distinct abnormalities characterizing relapsing-remitting MS (RRMS) and progressive MS (PMS), and with relevant associations with fatigue severity. Compared with healthy controls, patients with MS show altered top-down and bottom-up connectivity within the CAN. RRMS appears to be characterized by potentially adaptive or compensatory connectivity changes, whereas PMS shows more widespread and potentially maladaptive CAN disruption. AT seems able to modulate CAN connectivity, particularly in RRMS.

Discussion. Our findings support disruption of the CAN in MS, with distinct patterns in RRMS and PMS contributing to fatigue severity. These abnormalities may serve as potential biomarkers and therapeutic targets for autonomic dysfunction and fatigue in MS. The observed effects of AT suggest that neuromodulation of the CAN may represent a promising strategy for treating fatigue in MS.

Topic 04. Neuroimmune communication and neural control of immune responses

S.46 Urogenital And *Gastroenterological* Disorders In Multiple Sclerosis: Implications For The Clinic And Research

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Bladder and bowel dysfunctions are common in individuals with Multiple Sclerosis (MS), yet they remain significantly under-addressed. Up to 70% of patients will experience bladder disorders during the course of their disease, with a mean onset of 8 years.

These symptoms have a profound and devastating impact on the quality of life, often causing more distress to patients than the risk of medical complications themselves.

A systematic screening and appropriate evaluation are essential, based on the risk of complications. The more common symptoms include overactive bladder, urinary urgency incontinence, and constipation. Different therapeutic strategies exist and should be adapted to existing complications, anticipated risks, level of disabilities, and patients' preferences.

In this part, we'll review the mechanisms underlying bladder and bowel dysfunctions in MS. We'll also detail the recommended assessment. Special attention will be paid to identifying risk factors for complications that require dedicated management. Management strategies will be reviewed, including management of overactive bladder and voiding difficulties, as well as constipation and fecal incontinence. This section will cover simple lifestyle and dietary measures, non-invasive and pharmacological approaches, as well as advanced therapies.

A special time will be dedicated to clinical research perspectives, including clinical assessment, imaging, urodynamics, and therapeutics.

Join us for this workshop to master the latest algorithms and multidisciplinary approaches. By prioritizing the detection and management of these bladder and bowel disorders, we can directly enhance the quality of life and long-term health of our patients.

TOPIC 11. Emerging Concepts And Novel Perspectives In Autonomic Neuroscience

O.28 Characterizing Sweating Problems In Multiple Sclerosis: Insights From QSART, SUDOSCAN, And COMPASS-31

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Objective: To characterize sweating issues in people with multiple sclerosis (pwMS) using the Quantitative Sudomotor Axon Reflex Test (QSART) and SUDOSCAN.

Methods: In 75 pwMS, sweating symptoms were evaluated using the Composite Autonomic Symptom Score (COMPASS-31). Sweating function was assessed with QSART and SUDOSCAN.

Results: Symptomatic sweating problems were observed in 22 (29.3 %) pwMS. Pathological results of the QSART (sudomotor index (SI) >0) were identified in 13 (17.3 %) pwMS, while SUDOSCAN results showed pathology in 8 (10.7 %) pwMS. We found a positive correlation between the QSART volume of the foot and the SUDOSCAN

electrochemical skin conductance (ESC) results for the corresponding leg ($r = 0.282$, $p = 0.015$). pwMS with cervical spinal cord lesions had higher ESC values for the hand mean, left, and right (69.88±12.84 vs 76.15±9.29, $p = 0.022$; 69.88±12.82 vs 76.22±9.36, $p = 0.021$; and 70.33±13.00 vs 76.52±9.27, $p = 0.024$; respectively).

Conclusions: People with MS frequently experience sweating problems. Using various methods to identify sweating issues in pwMS reveals differences in the causes of these problems in pwMS.

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Topic 04. Neuroimmune communication and neural control of immune responses

O.29 Autonomic–immune Interactions And MRI Activity In Multiple Sclerosis

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Introduction: Reliable biomarkers capable of predicting future disease activity in multiple sclerosis (MS) remain limited. Given the close interaction between the autonomic nervous system and immune system, neurotransmitter receptor expression on immune cells may provide novel insights into mechanisms underlying disease activity. We investigated whether autonomic dysfunction, brainstem lesions, and neurotransmitter receptor expression on peripheral immune cells predict subsequent MRI activity in people with MS (pwMS).

Methods: In this prospective observational study, 64 pwMS underwent baseline clinical assessment, autonomic testing, serum neurofilament light chain measurement, brain

MRI, and peripheral blood immunophenotyping. Autonomic symptoms were assessed using COMPASS-31, while objective autonomic function was evaluated using the Composite Autonomic Scoring Scale (CASS). All measurements were obtained under

continuous non-invasive hemodynamic monitoring using the Task Force Monitor, CNSystems Medizintechnik AG, Austria. Evaluation of sudomotor function was performed using the Quantitative Sudomotor Axon Reflex Test (QSART). Flow cytometry was used to quantify expression of neurotransmitter receptors (ADRB2, nAChRα7, DRD3, DRD5) and cytokine receptors (IL1R1, IL1R2, IL1R8, IL23R) on

immune cell subsets. MRI activity was defined as the appearance of one or more new T2 lesions on follow-up MRI. Univariable and multivariable logistic regression analyses were performed to identify predictors of MRI activity.

Results: Twenty-three of 64 participants (35.9%) developed new MRI lesions during follow-up. The median time to new MRI lesions was 235 (161-293) days. Clinical autonomic measures, CASS scores, symptomatic dysautonomia, and serum neurofilament light chain levels were not associated with MRI activity. pwMS with MRI activity exhibited lower DRD3 (p=0.033) and IL23R expression (p=0.043) on helper T cells. In multivariable analysis, baseline brainstem lesions independently predicted MRI activity (OR 5.43, 95% CI 1.43–20.68, p=0.013), whereas higher DRD3 expression on cytotoxic T cells was independently associated with a lower risk of MRI activity (OR 0.93, 95% CI 0.87–1.00, p=0.035). The association was strongest within memory cytotoxic T-cell subsets.

Conclusion: Brainstem lesions and reduced DRD3 expression on peripheral cytotoxic T cells independently predict subsequent MRI activity in MS.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.30 Fingolimod-induced Cardiac Autonomic Changes In Patients With Relapsing-remitting Multiple Sclerosis Seem Reversible After Fingolimod-discontinuation

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Background and Objective: Continuous Fingolimod-therapy may affect cardiovascular-autonomic modulation (CAM) in patients with relapsing-remitting multiple-sclerosis (RRMS). It remains unclear whether any CAM-changes are reversible after Fingolimod-discontinuation. Therefore, we assessed CAM at rest and upon autonomic challenges before, during, and after Fingolimod-treatment.

Methods: In 11 RRMS-patients, we monitored RR-intervals (RRI), systolic and diastolic blood-pressure (BPsys, BPdia), and respiration at rest, during metronomic deep breathing (MDB), Valsalva-Maneuver (VM), and active standing-up, before and six hours after Fingolimod-initiation, after six months of daily Fingolimod-treatment, and after at least 5 months following Fingolimod-discontinuation. At rest, we calculated parameters reflecting total cardiac-autonomic modulation [RRI-standard-deviation (RRI-SD), RRI-coefficient-of-variation (RRI-CV), RRI-total-powers], sympathetic [RRI-low-frequency powers (RRI-LF), BPsys-LF-powers] and parasympathetic modulation [Root-Mean-Square-of-Successive-RRI-Differences (RMSSD), RRI-high-frequency powers (RRI-HF-powers, and baroreflex sensitivity (BRS). We also calculated expiratory-inspiratory-ratios (E/I-ratios) during MDB, Valsalva-ratios (VRs), and 30/15-ratios upon standing-up. We compared result-values using repeated analyses of variance or Friedman-tests with post-hoc analyses (significance: $p < 0.05$).

Results: Six hours after Fingolimod-initiation, RRIs and RRI-HF-powers were significantly higher, BPdia and Valsalva-ratios were significantly lower than pretreatment values. After six months of Fingolimod-treatment, RRI-SD, RRI-CV, RRI-LF-powers, RRI-total-powers, BRS, E/I-ratios, VRs, and 30/15-ratios were significantly lower than pretreatment values. After 5-20 (median 12, IQR 7-17) months of Fingolimod-discontinuation, these values had re-increased and no longer differed from pretreatment values. The other parameters (BPsys, Respiration, RRI-LF/HF-ratios, BPsys-LF- and HF-powers) did not differ between the four time-points.

Conclusions: Six months of Fingolimod-therapy attenuates cardiac-autonomic modulation at rest and during the above challenge-maneuvers. In our patients, these changes were reversible after Fingolimod-discontinuation.

13TH Symposium - DYSFUNCTION OF THE AUTONOMIC NERVOUS SYSTEM IN CARDIOVASCULAR DISEASE

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.47 Early Sympathetic Network Remodeling Precedes Structural Disease And Shapes The Arrhythmogenic Substrate In Desmoplakin Cardiomyopathy

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Rationale: Desmoplakin cardiomyopathy (DSP-CM) is characterized by malignant ventricular arrhythmias that often occur before fibrosis, chamber dilation, or systolic dysfunction. This temporal dissociation suggests that an arrhythmogenic substrate develops before overt myocardial remodeling. Because cardiac sympathetic neurons (SNs) are major regulators of excitability and conduction, we asked whether DSP mutations drive early remodeling of the cardiac sympathetic network. Consistent with a direct neuro-cardiac contribution, DSP protein was detectable in cardiac sympathetic ganglia.

Methods: We studied DspS311A knock-in mice modeling dominant DSP-CM (DspWT/S311A) and recessive Carvajal syndrome (DspS311A/S311A) at pre-structural and advanced disease stages. Sympathetic innervation across intact atria and ventricles was reconstructed in three dimensions after tissue clearing and high-resolution confocal imaging. Ventricular sections were used for quantitative analyses of axonal architecture, branching, and varicosities. Primary SN cultures from mutant mice were examined to determine whether neuronal abnormalities were cell autonomous.

Results: Sympathetic network remodeling was already evident at pre-structural stages in both genotypes, before detectable myocardial abnormalities. Rather than reflecting a uniform change in nerve density, remodeling involved a profound reorganization of network architecture. Mutant hearts showed axonal fragmentation, aberrant sprouting, and irregular varicosities. These changes were genotype specific. In DspWT/S311A hearts, hyperinnervation was diffuse and spatially homogeneous, while the physiological transmural gradient was retained, consistent with amplification of the native adrenergic framework. In DspS311A/S311A hearts, innervation was markedly heterogeneous, with epicardial hyperinnervation, endocardial hypoinnervation, and focal denervation. At advanced stages, sympathetic fibers extended into fibrotic areas, revealing active remodeling at the neuro-

fibrotic interface. Importantly, primary SNs from DSP-mutant mice recapitulated key structural abnormalities, supporting a neuronal-intrinsic component.

Conclusions: DSP mutations induce early and genotype-specific remodeling of the cardiac sympathetic network before structural cardiac disease becomes apparent. This remodeling generates spatial adrenergic heterogeneity and, with disease progression, neuro-fibrotic interfaces that may promote arrhythmogenic vulnerability. Our findings identify the sympathetic network as an early structural component of the arrhythmogenic substrate in DSP-CM and support genotype-informed neuromodulatory strategies.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.48 Neurovascular Interactions In The Ageing Heart

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Introduction: Aging is a major risk factor for cardiovascular dysfunction and is associated with vascular impairment, hypertrophy, fibrosis, and electrophysiological alterations. Endothelial cell dysfunction and senescence are hallmarks of aging; however, the contribution of the neurovascular interface to cardiac aging remains poorly understood. Given the close anatomical and functional alignment of vessels and nerves, we investigated whether neurovascular dysregulation contributes to age-associated cardiac pathology.

Methods: We assessed cardiac innervation in young and aged mice using histological and electrophysiological approaches. Endothelial cell-specific transcriptional changes were analyzed by bulk RNA sequencing, followed by validation using qPCR, protein analyses, and in vitro assays. Functional relevance was tested in genetic mouse models, including miR-145-deficient mice, and through pharmacological senolysis. In addition, we evaluated candidate regulators of endothelial senescence and neurotrophic signaling.

Results: Aging markedly reduced left ventricular innervation, particularly in perivascular regions, and was associated with increased arrhythmia susceptibility and reduced heart rate variability. Transcriptomic profiling of cardiac endothelial cells revealed enrichment of pathways linked to axon injury and neuronal death. The axon repellent factor Sema3a was upregulated in aged and senescent endothelial cells and identified as a target of miR-145, with miR-145 deficiency recapitulating the denervation phenotype. In parallel, we observed reduced expression of the neurotrophic factor VEGFB in aged endothelial cells, suggesting a loss of pro-innervation signals that contributes to cardiac denervation. Mechanistically, we identified the transcription factor ZBTB16 as a critical regulator of endothelial homeostasis: its loss induced vascular senescence and dysregulation of neurotrophic and axon guidance cues. Importantly, restoration of ZBTB16 expression in aged mouse hearts reduced endothelial senescence, improved cardiac function, and partially rescued innervation. Pharmacological clearance of senescent cells similarly reduced Sema3a expression and restored ventricular innervation and electrophysiological stability.

Together, these findings identify endothelial senescence as a central driver of cardiac denervation through an imbalance of axon repellent and neurotrophic signals. Targeting endothelial aging pathways, including ZBTB16-dependent mechanisms, may represent a strategy to preserve neurovascular integrity and cardiac function in aging.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.49 Superior Cervical Ganglion: A Driver Of Carotid Body Hyperexcitation In Hypertension

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Introduction: Carotid bodies (CBs) from spontaneously hypertensive (SH) rats display enhanced tonic activity and reflex sensitivity, contributing to exaggerated sympathetic outflow. We tested whether this hyperexcitability is driven by sympathetic innervation from the superior cervical ganglion (SCG), acting via direct effects on glomus cells or indirectly through vascular mechanisms.

Methods: Chemoreflex responses were evoked in situ (NaCN, 0.04%, 50–100 µL) in SH and Wistar rats under different conditions: SCG electrical stimulation (ES; 30 Hz, 2 ms, 10 V), unilateral SCG resection (SCGx), and CB microinjection of α1-adrenoceptor agonist (phenylephrine) or antagonists (prazosin, tamsulosin). Additional assessments included petrosal neuron activity, blood pressure measurements, Ca^{2+} imaging in isolated glomus cells, morphometry, and gene expression analysis.

Results: SCG stimulation increased CB-evoked sympathoexcitation by 40–50% in both strains ($P<0.05$). In contrast, SCGx markedly reduced this response in SH rats (−62%; $P<0.01$), with no effect in Wistar rats, and abolished basal chemoreceptor neuron activity in SH rats. In Wistar rats, phenylephrine enhanced reflex responses (+33%; $P<0.05$), while in SH rats, α1-blockade with prazosin (−26%; $P<0.05$) or tamsulosin suppressed CB sensitization and prevented SCG-induced effects. α1A- and α1B-adrenoceptors were localized to both glomus cells and CB vasculature (Figure 1). Phenylephrine also elicited Ca^{2+} transients in isolated glomus cells of Wistar rats.

In conscious SH rats, SCGx reduced CB-mediated pressor responses and lowered systolic blood pressure (−16 ± 4.85 mmHg). Morphometric analysis showed increased tyrosine hydroxylase-positive glomus tissue in juvenile SH rats ($P<0.05$), associated with upregulation of Epas1 (HIF-2α). Pharmacological inhibition of HIF-2α (PT-2385) attenuated CB responses.
Conclusion: These findings demonstrate that CB sympathetic innervation is tonically active and selectively enhances CB excitability in SH rats via α1-adrenoceptor-dependent mechanisms involving both vascular and direct glomus cell pathways. Targeting the SCG-CB axis may provide a novel therapeutic strategy for hypertension.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.50 - Sympatho-vagal Cross Talk In Health And Disease

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Although the autonomic nervous system is divided into two branches, the sympathetic and parasympathetic nervous system, significant interactions between these arms aim to finetune control of cardiac function. These interactions occur at both the central and peripheral levels. Peripheral interactions, operating through the primary neurotransmitters,norepinephrine and acetylcholine, are well established. These occur via activation of muscarinic and adrenergic receptors on the cardiac myocytes, as well as pre-synaptic mechanisms that affect the subsequent release of neurotransmitters. Increasingly,however, important interactions between europeptides, such as galanin and neuropeptide Y, and the primary neurotransmitters are also being recognized, including in inhibiting acetylcholine release from vagal terminals. Finally, key central interactions initiated by cardiac sensory afferents in each arm, have been reported over the past decade. These afferent fibers relay signals up the neuraxis to the brainstem and higher centers via the nodose and dorsal and other autonomic nuclei, producing feedback loops that can powerfully inhibit the opposite arm of the cardiac autonomic nervous system to maintain cardiovascular homeostasis.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.31 Pathways Involved In Regulating The Excitability Of HIPSC-derived Sympathetic Neurons

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Introduction: Postganglionic sympathetic neurons not only regulate target organs but also their own intrinsic activity and can be further modulated by parasympathetic neurons. This crosstalk and autoregulatory signalling have been implicated in cardiovascular disorders, with the majority of earlier work employing rodent models. Here, we have used human sympathetic neurons derived from induced pluripotent stem cells (hiPSCs), as a scalable human in vitro system with the aim to investigate these pathways.

Methods: hiPSC-sympathetic neurons were generated following a published protocol. Their lineage was assessed by immunostaining and Ca2+ imaging (nicotine application). We employed whole-cell patch clamp recordings in combination with pharmacological tools (Norepinephrine, UK14303, Carbachol, Tertiapin-Q and ML297). The relevance of the ion channels/receptors investigated were validated using published rodent stellate ganglia single cell RNAseq dataset.

Results: Efficient differentiation of hiPSCs into sympathetic neurons was confirmed using molecular characterisation for the expression of PHOX2B, DBH, TH, PRPH. Functional recordings revealed that the majority of cells were activated by nicotine and that they could be grouped according to their firing patterns (phasic and tonic) recapitulating the phenotype of rodent sympathetic ganglia. Agonists of 2 adrenergic and muscarinic receptors inhibited neuronal excitability evident by the increased hyperpolarisation and increase in rheobase. We identified a key role of G protein- coupled inward rectifier K+ channels (GIRK) downstream both pathway: the GIRK blocker Tertiapin-Q significantly reduced the 2 adrenergic and muscarinic responses, while the activator ML297 mimicked their action. Analysis of mouse thoracic sympathetic ganglia scRNA-seq dataset confirmed that both receptors and GIRK subtypes studied here are prominently expressed in native sympathetic neurons.

Conclusions: Overall, our data show that GIRK channels play an important role in the regulation of sympathetic neurons excitability and that hiPSC-derived neurons provide an attractive in vitro tool for drug discovery to study sympathetic autoregulation and parasympathetic-sympathetic crosstalk.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.32 Opposite Cardiac Autonomic Responses To Different Blood Components In A Rat Model Of Subarachnoid Hemorrhage

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Introduction: Subarachnoid hemorrhage (SAH) is a severe stroke subtype associated with high morbidity and mortality, and profound autonomic dysfunction.

Cardiac disturbances are among its most common systemic complications: rhythm abnormalities, from sinus bradycardia and tachycardia to ventricular arrhythmias, are documented in almost all patients during the acute phase. Moreover, cardiac arrhythmias following SAH are independently associated with increased mortality and poor neurological outcome. Although acute autonomic dysregulation driven by catecholamine release and increased intracranial pressure is considered central to these responses, the role of blood components in triggering rapid cardiac effects remains unclear. Therefore, we examined the acute heart rate (HR) responses elicited by whole blood (WB) and its fractionated components following injection into the subarachnoid (SA) space.

Methods: Adult male Sprague-Dawley rats were anesthetized with 2-2.5% isoflurane in O2. HR was continuously monitored from 2 min before to 10 min after SA injection (t0), in four treatment groups, receiving 300 µl of either autologous whole blood (WB; n = 9), artificial cerebrospinal fluid (aCSF; n = 8), autologous isolated red blood cells (RBC; n = 10) resuspended in aCSF, or autologous plasma (PLA; n = 11).

Results: WB injection induced a significant bradycardia compared to aCSF, evident at 90 s after injection (ΔHR from t0: WB, -33.18±8.19 vs aCSF, +0.44±2.54 bpm; $p<0.05$) and persisting to 5 min (WB, -15.4±7.9 vs aCSF, +1.3±2.5 bpm; $p<0.05$). When blood fractions were tested separately, RBC and PLA elicited opposite effects: HR increased progressively following RBC injection, whereas PLA decreased HR similarly to WB. Responses diverged from 150 s (ΔHR: RBC, +2.62±3.68 vs PLA, -8.31±2.73 bpm; $p<0.05$) through 10 min (RBC, +11.36±1.8 vs PLA, -6.51±4.95 bpm; $p<0.05$).

Conclusion: Plasma and red blood cells exert opposite effects on HR when injected separately into the SA space, pointing to distinct pathways of cardiac autonomic output in the acute phase of SAH. Future investigations should focus on identifying the specific neural circuits and molecular mediators that drive these cardiac responses, with the goal of understanding how they exert functionally opposing effects in the physiological context of this disease.

14TH Symposium - VAGUS NERVE STIMULATION IN EPILEPSY

TOPIC 05: Vagus Nerve Modulation And Bioelectronic Therapeutic Approaches

S.51 Biomarkers For Vagus Nerve Stimulation In Refractory Epilepsy

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Abstract Epilepsy is a serious neurological disorder associated with significant morbidity, psychiatric comorbidities, social stigma, and substantial healthcare costs. Approximately one-third of patients remain resistant to anti-seizure medications and may be considered for presurgical evaluation to assess eligibility for epilepsy surgery or, alternatively, neuromodulation therapies such as vagus nerve stimulation (VNS). Although VNS is an established treatment option for drug-resistant epilepsy, its clinical efficacy varies considerably between patients. Furthermore, its mechanisms of action remain incompletely understood, and reliable predictors of treatment response in individual patients are lacking.
There is therefore a clear need to optimize VNS therapy through a better understanding of its underlying mechanisms and the identification of biomarkers that can guide patient selection, treatment monitoring, and dose optimization. In this presentation, particular attention will be given to peripheral biomarkers, including laryngeal evoked motor potentials, as well as central biomarkers derived from EEG and pupillometry, which may provide valuable insights into target engagement, treatment response, and optimization of VNS therapy in patients with drug-resistant epilepsy.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.52 Neurophysiological Effects Of Vagus Nerve Stimulation In Humans: Vagal Microelectrode Recordings And Sympathetic Nerve Activity In Drug-resistant Epilepsy

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Introduction: Drug-resistant epilepsy (DRE) is associated with high rates of morbidity and mortality and elevated cardiovascular risk, including Sudden Unexpected Death in Epilepsy (SUDEP). Vagus nerve stimulation (VNS) is a neuromodulation-based therapy that reduces seizure frequency and burden in a proportion of patients with DRE. It is not well understood which vagal fibres are activated during clinical VNS and thus which may be responsible for improving seizure control. To date, autonomic function has only been assessed in DRE using indirect measures.

Methods: Ultrasound-guided vagal microneurography was performed in five awake DRE patients with chronically implanted VNS systems. Evoked compound nerve action potentials were recorded during the participant's clinical VNS settings, then amplitude was reduced to zero and increased in 0.25mA increments to their clinical setting at 1Hz. In a separate study muscle sympathetic nerve activity (MSNA) was measured from the common peroneal nerve in 16 patients with DRE and 16 healthy age- and sex-matched controls free from neurological and cardiovascular disease. In these studies, we calculated burst frequency (BF, bursts/minute), burst incidence (BI, bursts/100 heartbeats), neurovascular transduction, and sympathetic and cardiac baroreceptor sensitivity (BRS). Continuous non-invasive blood pressure (BP), respiration and heart rate were measured concurrently.

Results: Vagal recordings showed excitation of myelinated axons at currents of 0.75-1.0mA.

Notably, we observed recruitment of what appeared to be an unmyelinated axon at stimulation currents of 0.5mA. In the MSNA studies BF was significantly elevated in DRE patients (37.0±7.1 bursts/min) compared to controls (30.8±6.9 bursts/min; p = 0.0166). Systolic BP was also significantly elevated in DRE patients (131.4±17.7 mmHg) compared to controls (116.2±5.2 mmHg; p=0.027). Additionally, sympathetic BRS was significantly lower in participants with DRE compared to controls, with medians of -0.33 and -1.73, respectively (p=0.024) but no differences were observed in cardiac BRS between groups.

Conclusion: MSNA and systolic BP were both elevated in participants with DRE which may contribute to the elevated cardiovascular risk associated with DRE. Activation of C-fibres were observed more frequently and at lower stimulation amplitude then has been previously reported, challenging the assumption that these fibres are not responsible for clinical VNS efficacy.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.53 Vagus Nerve Activity Modulations During Absence Seizures, NREM Sleep, Wake, And Hypercapnia In Epilepsy Rat Models

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Epilepsy is one of the most common chronic neurological disorders and remains drug-resistant in approximately one-third of patients. In these individuals, recurrent seizures may be associated with long-term autonomic alterations and severe complications, including sudden unexpected death in epilepsy (SUDEP). Vagus nerve stimulation (VNS) is an established adjunctive therapy, and current closed-loop approaches mainly rely on ictal tachycardia detection. However, cardiac responses are highly variable across patients, epilepsy syndromes and seizure types, limiting the universality of this strategy. Direct recordings of cervical vagus nerve activity (VNA) may provide a complementary peripheral window into seizure-related autonomic dynamics and help refine future adaptive neuromodulation strategies.

This work aimed to characterize cervical VNA in Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a validated model of absence epilepsy, and to determine how vagal activity is modulated by spontaneous seizures, epilepsy duration, vigilance state and respiratory stress. Chronic cervical VNA recordings were performed in freely moving GAERS and non-epileptic control rats, combined with EEG, video and cardiorespiratory monitoring. This approach allowed the identification of spike-and-wave discharges, behavioral state and physiological responses during baseline recordings and hypercapnic challenge.

Spontaneous absence seizures were associated with a reproducible increase in VNA, indicating that even non-convulsive seizures engage vagal/autonomic pathways. This ictal vagal modulation was influenced by age and/or cumulative seizure burden, suggesting progressive alterations in seizure–autonomic interactions. Beyond seizures, VNA was also shaped by physiological state. In control and epileptic animals, vagal activity differed between wakefulness and non-rapid eye movement sleep, however VNA was lower during NREM sleep in in GAERS. During hypercapnia, GAERS displayed abnormal cardiorespiratory responses compared with controls, supporting the presence of impaired autonomic adaptation to respiratory stress.

These findings indicate that cervical VNA contains information about seizure occurrence, vigilance state and chemoreflex-related autonomic regulation in chronic absence epilepsy. VNA may therefore represent a promising peripheral signal to better understand seizure–autonomic interactions and to support the development of more individualized, physiology-driven closed-loop neuromodulation strategies.

TOPIC 05. Vagus nerve modulation and bioelectronic therapeutic approaches

S.54 Hypercapnic Cardiorespiratory Responses In Epileptic Rat Models

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Epilepsy is associated with respiratory and autonomic disturbances that may contribute to increased vulnerability to Sudden Unexpected Death in Epilepsy (SUDEP). Generalized tonic-clonic seizures are a major risk factor for SUDEP, whereas absence seizures are not typically associated with the same level of risk. Postictal respiratory dysfunction, including apnea, hypoventilation, and impaired recovery from hypercapnia, is considered a major contributor to SUDEP. Central respiratory chemoreception refers to the detection of CO_2/H^+ changes by specialized brainstem networks that adjust ventilation to maintain blood gas and pH homeostasis. Impaired responses to hypercapnia may therefore reveal seizure-type-specific dysfunction in central chemoreception and its integration with cardiovascular autonomic control.

Hypercapnic ventilatory response testing in rat models of epilepsy showed seizure-type- and disease-stage-dependent alterations in cardiorespiratory regulation. In kainic acid (KA) rats with convulsive epilepsy, hypercapnia-induced ventilatory and cardiac responses were blunted, with impaired heart rate variability reactivity and disrupted breathing-heart rate coupling. In contrast, Genetic Absence Epilepsy Rats from Strasbourg (GAERS) maintained the ventilatory response, with faster post-challenge normalization and intermediate cardiac changes. Longitudinal testing in KA rats further showed that impairment of the hypercapnic cardioventilatory response emerges abruptly during epileptogenesis, with CO_2-evoked breathing alterations preceding heart-rate abnormalities. Preliminary unpublished immunohistochemical analyses suggest altered activation of Phox2b-expressing chemosensory neurons and changes in the galaninergic subset after hypercapnia, supporting a role for neuropeptide-defined RTN/brainstem populations in adaptive CO_2 responses.

Since central respiratory chemoreception interacts with vagal afferent and efferent pathways, these findings raise the possibility that epilepsy-related chemoreflex impairment may extend to vagus nerve function. This provides a rationale to test whether vagus nerve stimulation can improve CO_2-evoked respiratory-autonomic coupling and reduce cardiorespiratory vulnerability.

Together, these data suggest that hypercapnic cardioventilatory testing may provide a sensitive translational readout of autonomic dysfunction in epilepsy. Future studies will determine whether long-acting neuropeptide-based strategies, alone or combined with neuromodulation, can restore chemosensory network resilience.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.33 Convulsive Seizures Alter Autonomic Balance, Increase Cardiac Output And Arterial Pressure And Induce Arrhythmias In Non-anaesthetized Sheep

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INTRODUCTION: Preclinical and human studies suggest that ictal and interictal modulation of the sympathetic and parasympathetic systems contribute to cardiovascular changes that may induce sudden unexpected death in epilepsy. We therefore developed and characterised a novel model of convulsive seizures induced by the pro-convulsant pentylenetetrazol (PTZ) in non-anesthetised sheep. We then investigated the effects of seizures on cardiovascular and autonomic function.

METHODS: Merino ewes were instrumented to record arterial pressure, heart rate, the electroencephalogram and electrocardiogram, and either cardiac output or cardiac and renal sympathetic nerve activity (SNA). Arterial blood samples were collected to assess blood biochemistry. Seizures were induced in non-anesthetised sheep by intravenous infusion of PTZ (5.0 mg/kg/min for 4 minutes).

RESULTS: PTZ induced consistent generalized tonic-clonic seizures that followed a reliable sequence and were associated with abnormal activity on the electroencephalogram. Seizures increased mean arterial pressure (79.1±4.5 mmHg to 128.5±5.6 mmHg, $P < 0.0001$) and cardiac output (4.1± 0.2 to 7.9±0.5 L/min, $P <0.0001$) at 10 min post-seizure; these remained significantly above baseline for 60 min (both n=12). Heart rate variability decreased (4826.1±766.6 to 210.9±97.7 ms, n=6, P=0.0155) at 10 minutes postictally and corrected QT interval increased (399±9.1 to 449.7±11 ms, P=0.003) at 30 minutes postictally. Seizures increased cardiac SNA (682±86 to 7558±3955 spikes/minute, n=4, P=0.007), while renal SNA decreased (4296 ± 784 to 1139 ± 284 spikes/min (P=0.047). Arterial partial pressure of oxygen was not significantly changed but partial pressure of carbon dioxide was significantly reduced at 10 minutes (34.4 ± 0.6 to 27.4 ± 1.5 mmHg, P = 0.0001) and 30 minutes post-seizure (30.1 ± 0.8 mmHg, P = 0.0386). During seizures and for 15-20-min postictally, atrial and ventricular ectopy was observed including atrial triplets and periods of ventricular trigeminy in 9 out of 12 sheep. There was also evidence of premature atrial/ventricular beats and sinus arrhythmia.

CONCLUSION: Seizures induced by PTZ in non-anaesthetised sheep were reproducible and behaviourally similar to the changes seen in human epilepsy. Seizures caused autonomic and cardiovascular disturbances, including ictal and postictal tachycardia, repolarisation abnormalities and arrhythmias, which may contribute to an increased risk of sudden unexpected death in epilepsy.

15TH Symposium - NEUROPEPTIDES AS CORE INTEGRATORS OF CARDIAC AUTONOMIC FUNCTION

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.55 Calcitonin Gene-related Peptide (CGRP) As A Protective Neuropeptide In Cardiovascular Protection

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Introduction: Calcitonin gene-related peptide (CGRP) is a potent microvascular vasodilator neuropeptide [1]. This group has investigated the activity of a long acting CGRP agonist (in collaboration with Dr Anette Sams, Epoque Pharma) in preclinical studies of hypertension and pressure-overload-induced heart failure where it is protective [2]. The long acting agonist was protective for up to several weeks against cardiac fibrosis, remodelling and loss of heart function [2]. In further studies we have provided evidence that the protective action of CGRP is independent of nitric oxide [3].

Methods: This group's recent study is that of a murine model of myocardial infarction (MI) We have investigated adult wildtype wildtype (WT) and α CGRPKO mice for up to 72h after left anterior descending ligation of the coronary artery. In further studies we investigated the effect of the CGRP agonist giving over 1-4 days after MI induction on the resulting heart function and lesion up to 21 days.

Results: Inflammatory biomarkers including the neutrophil biomarker MPO were measured at 24 and 72h post-MI in WT and α CGRP KO mice. Genetic deletion of α CGRP enhanced the inflammatory response to cardiac injury post-MI. CGRP KO mice developed enhanced cardiac and pulmonary weight (oedema) 24h and 72h post-MI ($P<0.05$ vs sham) in addition to enhanced left ventricular neutrophil (MPO) accumulation 24h post-MI when compared to WT mice. In the 21 day study the early administration of the CGRP agonist was protective.

Conclusions: These results indicate that CGRP is involved at early timepoints after MI in protecting against the inflammatory impact of MI. This is in keeping with the concept that exogenous administered CGRP is protective during the early inflammatory phase after MI leading to benefits in the later phases involving cardiac fibrosis, remodelling and heart function.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.56 Regulation Of Cardiac Norepinephrine By Closed-loop Feedback Modulation

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Introduction: Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Over 500,000 cardiac surgeries and procedures, which require detailed cardiac diagnostics and intense monitoring, are performed to treat arrhythmias and structural heart disease in the US each year. Together, these carry a morbidity and mortality risk of 1-30%, depending on a patient's comorbidities. Heart failure is known to result in elevated myocardial norepinephrine (NE) levels which indicate a worse prognosis and are associated with ventricular arrhythmias, cardiac mortality, and sudden cardiac death. Therefore, NE can serve as an important biomarker of the status of cardiac disease. Cardiac disease disrupts not only heart muscle, but also the cardiac nervous system. Neural control of the heart reflects a hierarchy of interdependent reflex loops involving intrathoracic and central nervous system neural networks. At rest, parasympathetic cholinergic input dominates. During high levels of stress, catecholaminergic sympathetic control becomes dominant. Both the progression of heart failure and the potential for sudden cardiac death are associated with excessive sympatho-cardiac excitation with resultant elevated myocardial NE. Previous work showed direct current nerve block of sympathetic cardiac innervation mitigates NE levels under stress.

Methods: Here we show that a closed-loop fuzzy logic controller, using real-time norepinephrine (NE) measurements via fast-scanning cyclic voltammetry as a feedback signal, can drive direct current (DC) electrical nerve block of the paravertebral sympathetic chain to achieve graded, on-demand reductions in cardiac NE release in both healthy and chronically infarcted pigs.

Results: Controller-directed block produced significant reductions in peak and sustained NE release at target setpoints in both animal models, with corresponding improvements in left ventricular systolic pressure recovery post-pacing.

Conclusions: These findings establish bioelectronic closed-loop sympathetic nerve block as a viable, reversible alternative to surgical sympathectomy. By delivering an electrical "on-demand sympathectomy", refractory ventricular arrhythmias time and post-infarction sympathetic dysregulation can be managed in real-time, limited side effects and applying the ultimate patient-specific treatment.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.57 Glucagon-like Peptide 1 As A Peptide Modulator Of Cardiac Electrophysiology

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely prescribed for type 2 diabetes and obesity. Although these agents generally improve cardiovascular outcomes, they are consistently associated with an increase in heart rate, the underlying mechanism of which remains poorly understood.

Methods: We used a large animal model (female landrace pigs) and combined in vivo and ex vivo approaches, including pharmacological interventions, electrophysiology, and high-resolution mass spectrometry, to investigate how GLP-1 increases heart rate.

Results: In anaesthetized pigs, the chronotropic response to GLP-1 persisted despite cervical vagotomy, adrenergic blockade (α, β, or combined α-β), ganglionic blockade with hexamethonium, and inhibition of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels using ivabradine. In isolated perfused pig hearts, GLP-1 similarly increased heart rate, an effect that was abolished by GLP-1 receptor antagonism. Electrophysiological analyses in vivo and in isolated hearts localized GLP-1's effects to the atria and conduction system. In isolated sinus node preparations, GLP-1 shortened the pacemaker action potential cycle length and shifted the leading pacemaker site, independent of HCN channel inhibition. These findings suggest a direct cardiac action of GLP-1. Supporting this, single-nucleus RNA sequencing demonstrated GLP-1 receptor expression in porcine pacemaker cells. Furthermore, phosphoproteomic analysis of sinus node tissue revealed GLP-1-induced phosphorylation changes in sarcoplasmic reticulum calcium-handling proteins known to regulate heart rate.

Conclusion: GLP-1 exerts direct chronotropic effects via GLP-1 receptors in sinus node pacemaker cells by modulating action morphology and pacemaker site activity through calcium-dependent signaling, characterized by PKA-mediated phosphorylation of key calcium cycling proteins involved in pacemaking. Targeting the pacemaker calcium clock may represent a strategy to mitigate elevated heart rate in patients receiving GLP-1 RAs.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.58 Npy Signalling In Human Cardiomyocytes And The Parallels In Patients Experiencing Myocardial Infarction

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Acute myocardial infarction (AMI) and chronic systolic heart failure (CHF) result in high levels of cardiac sympathetic stimulation, which is a poor prognostic indicator. Whilst beta-blockers improve mortality in these conditions by preventing the action of the main neurotransmitter norepinephrine, a substantial residual risk remains. Recently, we have identified the sympathetic co-transmitter neuropeptide-Y (NPY) as being released during ST-elevation myocardial infarction (STEMI), leading to larger infarcts(1) and life-threatening ventricular arrhythmias(2) in both animal models and patients. In patients with STEMI, admission venous NPY levels correlate with long term risk of CHF and death(3). Moreover, in patients with CHF of different aetiologies across a range of ejection fractions, NPY levels correlate with mortality above that of BNP(4), as well as prognosis during ventricular tachycardia (VT) storm(5). However, given the range of NPY receptors, species differences in expression and second messenger coupling, a significant challenge remains to target appropriate drug therapy to this pathway, with divergent results being reported in different animal models. In this talk, I will present unpublished preliminary data suggesting that human induced pluripotent stem cell derived cardiomycytes (hiPSC-CMs) studied in isolation, monolayers and 3D spheroids recapitulate key receptor, electrophysiological and structural responses to NPY which functionally correlate with the those observed in patients being treated for STEMI. This may therefore provide an appropriate platform to develop therapeutic intervention targeting this pathway.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.34 A Combination Of GLP1 Receptor Agonist And P2X3 Receptor Antagonist Ameliorate High Blood Pressure And High Blood Sugar In A Novel Rat Model Of "glucotension"

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Aim: Diabetes is the fastest-growing disease in New Zealand. Most (75%) patients with T2D have high blood pressure (BP), and half of BP patients exhibit high blood glucose (BG) a condition we call "glucotension". Glucagon-like peptide type-1 (GLP-1) regulates blood glucose whereas antagonism of P2X3 receptors decreases blood pressure, particularly in conditions of overactive peripheral chemoreceptors. However, the efficacy of this combination of drugs has not been tested in glucotension. Thus, we hypothesised that a GLP-1 agonist combined with a P2X3 receptor antagonist will restore blood pressure and blood glucose in glucotension.

Methods: We developed a novel rat model of glucotension induced using a high-fat diet (HFD) and streptozotocin (STZ; 100mg/kg delivered via Osmotic pump) in spontaneous hypertensive rats (SHR). GLP1 receptor agonist (Exendin-4; 5ug/kg/Oral) and P2X3 receptor antagonist (AF130; 30mg/kg/Oral) given chronically in combination while assessing chemoreflex, blood glucose, glucose tolerance test (GTT), cognitive function (Barnes Maze, Novel object recognition tests), BP and renal SNA were assessed via radio-telemetry. Cardiac (ultrasound) and respiratory (plethysmography) functions were also studied.

Results: Our results showed acute bolus of Exendin-4 & AF-130 attenuated the chemoreflex evoked SNA response along with a reduction in BP in HFD+STZ fed conscious SHRs ($p<0.05$). Chronic drug treatment showed an improvement in GTT, fasting BG and BP level compared to control groups along with reduced systolic dysfunction ($P<0.05$) and improved triglyceride levels and cognitive function.

Conclusion: A GLP-1 receptor agonist and P2X3 receptor antagonist ameliorated the hypertension and hyperglycaemia in a novel model of glucotension. We propose that the combination of GLP-1 receptor agonist and P2X3 receptor antagonist provides a new way to control glucotension potentially via modulating SNA.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.35 Oxygen Not Included: Chemoreflex Modulation By GLP-1 And A-MSH In Cardiovascular Disease

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Introduction: Traditionally viewed solely as arterial hypoxia sensors, mammalian carotid bodies are gaining wider recognition as multimodal chemosensory organs responding to a range of signals in the circulation. In cardiometabolic diseases such as hypertension and type 2 diabetes, aberrant afferent activity from the carotid body contributes to chronically elevated sympathetic tone despite preserved arterial oxygenation. What factors drive heightened arterial chemoafferent activity in disease states, particularly in the absence of arterial hypoxaemia, remain poorly understood.

Methods: To identify candidate mediators, we performed an unbiased RNA-seq screen of carotid bodies in the Spontaneously Hypertensive Rat (SHR) model of arterial chemoreflex sensitisation. Functional relevance of identified hits was tested using a range of in vitro and in situ assays.

Results: We discovered the presence of glucagon-like peptide-1 (GLP-1R) and melanocortin-4 (MC4R) receptors in animal and human carotid body chemosensory cells.1,2 Experimentally, GLP-1R activation in the carotid body attenuated arterial chemoreflex-evoked sympathetic and pressor responses,1 whilst MC4R stimulation using α-MSH (endogenous agonist) augmented carotid body chemoafferent drive and arterial chemoreflex sensitivity.2 GLP-1R downregulation and MC4R upregulation in the carotid body were linked to arterial chemoreflex sensitisation and increased sympathetic tone in the SHR.

Conclusion: GLP-1R and MC4R represent druggable targets in arterial chemoreceptors for managing sympathetic overactivity in cardiometabolic disease, warranting further translational studies. Our findings also suggest a putative role of arterial chemoreceptors in neural control of energy homeostasis through non-hypoxic mechanisms.

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16TH Symposium - MULTIPLE SYSTEM ATROPHY: FROM BENCH TO BEDSIDE

TOPIC 11. Emerging concepts and novel perspectives in autonomic neuroscience

S.59 Msa: Experimental Insights Into Mechanisms Of Disease Progression

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Introduction: Multiple system atrophy (MSA) is a rapidly progressive neurodegenerative disorder characterized by oligodendroglial α-synuclein accumulation, parkinsonism, cerebellar ataxia, and autonomic failure. Although glial cytoplasmic inclusions define the disease pathologically, the mechanisms linking oligodendroglial α-synucleinopathy to selective neuronal loss and clinical progression remain incompletely understood.

Methods: Disease mechanisms were investigated using complementary experimental approaches, including therapeutic strategies targeting α-synuclein oligomerization, patient-derived cellular models, PLP-αSyn mice, post-mortem tissue analyses, transcriptomics, neuropathology, and preclinical intervention studies.

Results: Across these approaches, MSA emerges as a disorder driven by interacting pathogenic processes rather than by a single molecular defect. Targeting α-synuclein oligomerization supports the relevance of early toxic α-synuclein species and proteostasis as disease-modifying targets. Patient-derived cellular models reveal mitochondrial abnormalities, altered stress responses, and increased vulnerability to oxidative damage, suggesting that impaired bioenergetics may create an intrinsic susceptibility that precedes overt neurodegeneration. In parallel, hypoxic stress, potentially linked to autonomic, cardiovascular, and respiratory dysfunction, may amplify mitochondrial injury, oxidative damage, and α-synuclein pathology, providing a clinically relevant link between systemic dysfunction and brain degeneration. Altered iron homeostasis provides another converging mechanism, promoting oxidative stress, influencing α-synuclein aggregation, and representing a therapeutically tractable pathway. In experimental MSA models, oligodendroglial α-synucleinopathy is associated with early and progressive disruption of metabolic, myelin, synaptic, lysosomal, cytoskeletal, and immune-related pathways. These changes are regionally patterned, supporting the concept that vulnerability reflects the interaction between local cellular environment, metabolic demand, oligodendroglial dysfunction, microglial responses, aging, and systemic stress. Neuroinflammatory pathways, including maladaptive microglial activation, further emerge as active contributors to pathology, with therapeutic modulation reducing α-synuclein pathology, gliosis, and neuronal damage in experimental settings.

Conclusion: These findings support a view of MSA as a dynamic, multisystem neurodegenerative process in which glial α-synucleinopathy initiates cellular stress responses shaped by regional vulnerability and amplified by metabolic, inflammatory, iron-related, and systemic factors. Understanding how these mechanisms interact over time and across vulnerable brain regions is essential to define the biological logic of disease progression and to identify points at which this process may be therapeutically modified.

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TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.60 Advances In AI-supported MSA Diagnostics And Biomarker Research

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Introduction: Multiple system atrophy (MSA) has overlapping clinical phenotypes with other neurodegenerative disorders that create diagnostic dilemmas, particularly early in the disease course. Novel artificial intelligence supported diagnostic algorithms have shown significant promise in diagnosing patients with MSA, even in the prodromal disease state.

Methods: After consent, patients with pure autonomic failure, MSA, PD, DLB and completed neurologic examinations, medical history review, cognitive evaluation, orthostatic vital signs and neurodegenerative disease questionnaires. Skin biopsies were taken from the distal leg, distal thigh and posterior cervical sites with immunostaining of phosphorylated alpha-synuclein (P-SYN) and protein gene product 9.5 (PGP9.5). Slides were digitally scanned and quantitative AI-supported pathological analysis of P-SYN deposition provided quantitative data by location, amount and nerve fiber subtype involvement. Clinical, demographic and pathological data were combined using unbiased weighted cluster analysis into an algorithm to differentiate the two disease states based on a training data set, with blinded prospective testing in a validation cohort.

Results: The training data set included 15 patients each with MSA, PD and DLB. The validation cohort included an independent group of 30 patients each with MSA, PD, DLB and PAF. The training set identified demographic, clinical and pathological data that could be integrated into a predictive algorithm for diagnosis. The algorithm correctly identified 14/15 PD, DLB and MSA in the training set. In the validation data set, cases were correctly identified with> 90% accuracy in diagnosing MSA, PD and DLB. Patients with PAF that would phenoconvert to MSA were correctly identified in 5/5 cases.

Conclusion: Skin biopsy detection of phosphorylated alpha-synuclein, with AI-supported biomarker analysis, has high diagnostic sensitivity and specificity across a range of synucleinopathies.

S.61 Cure MSA

Margherita Fabbri (University Hospital Toulouse, France)

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.62 Care for people living with MSA

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Multiple system atrophy (MSA) progresses rapidly and combines severe motor impairment with prominent autonomic dysfunction, making multidisciplinary care essential. The pandemic exposed existing gaps in direct patient support but also accelerated the uptake of digital health tools and telemedicine. This presentation outlines practical care models for MSA, highlighting recent advances in managing orthostatic hypotension, urogenital voiding dysfunction, and chronic pain. It further examines how structured decision-making within advanced care planning can help address "total pain" in rapidly progressive, life-limiting conditions.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.36 Cardiovascular Autonomic Failure In Multiple System Atrophy: Multimodal Characterization And Longitudinal Progression In 211 Patients From The MSA-BO Cohort

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Background: Cardiovascular autonomic failure (CAF) is a core feature and a major contributor to morbidity in Multiple System Atrophy (MSA). Despite the clinical importance, its characterization and longitudinal progression remain limited.

Objectives: To longitudinally characterize CAF in MSA through multimodal instrumental evaluation.

Methods: This is a retrospective and prospective study: 211 MSA patients from the MSA-BO cohort underwent standardized cardiovascular reflex tests (83 females; mean age 62.0±8.3years; mean disease duration at first test, T0: 4.6±2.7years; 54 patients within the first three years). Seventy-three patients underwent the same evaluation after at least 8 months (T1: mean disease duration 7.6±3.7years). During head-up tilt test, plasma norepinephrine (NE) levels were collected in 111 patients and cardiac^123I-MIBG scintigraphy was performed in 77.

Results: At T0, neurogenic orthostatic hypotension (nOH) was present in 144/211 patients (68%), including 37/54 (69%) evaluated within the first three years. Among patients without nOH, Valsalva maneuver abnormalities were common, occurring in 45/211 patients (21%), with delayed OH also observed in a subset of cases. Longitudinal evaluation showed progression, with 4/18 patients with isolated Valsalva abnormalities developing nOH and others showing worsening cardiovagal indices. Overshoot was absent in most patients at both T0 and T1, while pathological Valsalva ratio was observed in about half of the cohort and could newly emerge during follow-up. MIBG scintigraphy was normal in 65/77 patients, and plasma NE showed a reduced orthostatic increase.

Conclusions: These findings indicate early sympathetic impairment, mainly of central (pre-ganglionic) origin, in MSA, followed by progressive parasympathetic dysfunction. Post-ganglionic sympathetic involvement was observed in 16% of patients. A thorough characterization of CAF in MSA may support appropriate treatment and help define phenotypes with potentially different disease courses and prognoses. CAF appears to worsen over time and may represent a meaningful marker of disease progression.

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

O.37 Pain In Multiple System Atrophy: A Healthcare Professionals' Survey

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Introduction: Pain is a frequent non-motor symptom in people with MSA, whose recognition and management remain heterogeneous due to the lack of disease-specific screening tools and treatment guidelines. Here we aim to appraise the current knowledge, screening and treatment habits on pain in multiple system atrophy (MSA) among allied healthcare professionals (HCPs).

Methods: Informed by the pre-existing literature, a panel of pain, movement and autonomic disorders experts developed a survey to explore prevalence and characteristics, screening and treatment habits on pain in MSA. The questionnaire was disseminated among

HCPs through MSA professional and advocacy networks and was accessible online from January 7th to February 15th, 2026.

Results: One hundred and ninety HCPs accessed the survey. After removing duplicated and incomplete entries, 140 questionnaires were retained for final analysis. Participants were mostly doctors, nurses and physiotherapists (74%, 12% and 9%) based in Europe (85%) and North America (12%). According to HCPs, pain affected mostly the head/neck/shoulders, back, and legs (90%, 66%, and 56% respectively). Musculoskeletal, followed by pain due to postural deformities and dystonia (73%, 63% and 59%) were the most common pain types. Pain detection relied on medical history (53%) and semi-structured questions (41%), while validated pain questionnaires were rarely used (8%). Pain was managed by pain-specific pharmacological and non-pharmacological measures (85% and 81%) and by adjusting the dopaminergic medications or optimizing the symptomatic treatment of non-motor features (56% and 61%). Gabapentinoids, antidepressants, and paracetamol were the most used medications (78%, 70%, and 63%), while physical therapy, massage, and mindfulness/relaxation the most common non-pharmacological approaches (85%, 43%, and 22%). Time constraints and the lack of disease-specific recommendations were the most common barriers for pain detection and treatment in daily practice.

Conclusions: Aligning the experience of persons with MSA, pain was reported to affect most the neck, shoulders, back and legs, with musculoskeletal pain being the most common type of pain. Treatment habits partially diverged across HCPs' and patients' experiences. The results of this survey, along with the patients' experience and evidence from the pre-existing literature, will inform the development of tailored screening tools and treatment strategies for pain in MSA.

17TH Symposium - RETHINKING THE DEFINITION OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM

S.63 The Emergence Of The Terms Sympathetic And Parasympathetic And Subsequent Effects On Clinical Medicine.

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Introduction: Sympathy as material causality in medical thinking is alive and thriving.

Methods: Historical, cultural and contemporaneous epistemological practices as well as original scientific writings leading to sympathetic and parasympathetic concept formation were critically reviewed.

Results: Anatomically the vagus nerve was separated early on from the sympathetic ganglionated chain. The visceral ganglionated nerves were crowned as the sympathetic nerves and became independent centers of reflex action. 19th century neurophysiological experimental data denied the existence of an independent sympathetic nervous system. Without detailed knowledge of visceral afferents and central regulatory centers, separation into somatic or voluntary and visceral or involuntary nerves led to the concept of a separate “autonomic nervous system”. Common peripheral anatomic, pharmacological dissection and animal experimental data led to the separation of the cranial and sacral fibers from the rest of the spinal visceral fibers. The “parasympathetic” nervous system was born.

Conclusions: The concept of anatomically, pharmacologically, and physiologically segregated and antagonistic sympathetic and parasympathetic nervous systems continues to be defended by clinicians and scientists. Clinicians for the most part continue to believe the sympathetic and parasympathetic nerves as forming a separate, autonomic nervous system. This conceptual framing continues to be a placeholder explaining many ailments, like for example “dysautonomia” just like in the 17th century.

TOPIC 11. Emerging concepts and novel perspectives in autonomic neuroscience

S.64 The Sympathetic And Related Systems Of Nerves

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In 1905, John Langley decided to call « parasympathetic » what was not « sympathetic » in his newly coined “autonomic nervous system” and later cursorily alluded to a mutual antagonism of the two divisions. This dichotomic view of the neural control of the viscera rapidly solidified into a mnemonic landscape, where data were fitted as they could, at the cost of caveats, approximations and occasional misrepresentations. By approaching the autonomic nervous system through its ontogeny, I will argue that, at the level of detail where the sympathetic outflow appears unified, the “parasympathetic” breaks down into a mosaic of pathways, as unrelated in the identity of their neuronal components as they are in their physiological function − harking back to the pre-dichotomic view of Langley himself, in his monography on "The sympathetic and related systems of nerves" (1898). I will also point to overlooked commonalities among visceral and somatic outflows, at both genetic and physiological levels, and accordingly propose a reclassification of all efferents, orthogonal to the “autonomic” category.

TOPIC 07. Molecular and systems-level mapping of autonomic circuits and brain–body integration

S.65 Novel Insights Into Neuro-humoral Aspects Involved In Urinary Bladder Control

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Introduction: Peripheral regulation of the urinary bladder (UB) is classically known to be dependent on the autonomic nervous system. Central areas in the pons, midbrain, hypothalamus and cortex are involved in the micturition control, modulating the innervation to the bladder. This study focused to investigate novel brain areas and humoral-dependent mechanisms involved in UB control. Methods: Adult female (~250 g) or male Wistar rats (~450 g) with stainless steel guide cannulas implanted into the 4th brain ventricle (4th V) or lateral preoptic area (LPA) or shell Nucleus Accumbens (sNAcc) 7 days prior to the experiments were isoflurane anesthetized and subjected to cannulation of the femoral artery and vein for mean arterial pressure (MAP) and heart rate recordings (HR). Left renal blood flow was recorded by Doppler flowmeter to determine renal conductance (RC). The UB was cannulated for intravesical pressure (IP) measurement. After the baseline MAP, HR, RBF and IP recordings for 15 min, injections of carbachol (into the 4the V) or angiotensin-(1-7) [(Ang-(1-7) into the LPA] or GABA (into the sNAcc) or saline were performed and the variables were measured for additional 30 min. Data are as mean±SEM and submitted to Student´s t test (P<0.05). Results: Carbachol injection into the 4th V increased IP (42±6% vs. -11±6% saline, n=6) with peak response at 30min after carbachol and yielded no changes in MAP, HR and RC. The IP-evoked response by carbachol elicited plasma vasopressin release and was also abolished by iv. injection of V1a receptor antagonist. Ang-(1-7) injection into the LPA increased IP (187±37% vs. -2±2% saline, n=6) and elicited no changes in MAP, HR, and RC. GABA injections into the shell NAcc evoked a significant fall in MAP (-63±3 vs. -4±1 mmHg, saline, n=6), HR (-99±7 vs. 2±1 bpm, saline), and significantly increased IP (169±3% vs. 5±3%, saline) and RC (171±9% vs. 4±2% saline). Conclusion: The findings demonstrate that cholinergic neurons in the medulla can increase IP dependent on vasopressin release that acts in the UB. LPA contains neurons that can be activated by Ang-(1-7) to increase IP. GABAergic neurons in the sNAcc are involved in the micturition control pathways.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.66 The Autonomic Nervous System: Just A Bunch Of Central Pattern Generators?

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I suggest that it is time to expand the role of the autonomic nervous system to any part of the nervous system that contains a central pattern generator. By definition, a central pattern generator, or simply CPG, is a collection of neurones - usually located within lower parts of the central nervous system such as the basal ganglia, hypothalamus, brainstem and spinal cord - that produces a stereotyped motor output: a set of sequential, highly ordered, motor commands that, once initiated, can run independently of conscious awareness. Examples of CPGs include those subserving respiration, swallowing and locomotion. The outputs of all CPGs can be modified by sensory inputs, which ensure normal smooth operation of the CPG or allow adaptation to a particular sensory context. Unlike respiration, which operates continuously, both swallowing and locomotion are usually initiated by voluntary effort, but both can also be triggered by events that are outside conscious awareness. Like locomotion, respiration (and the oral, pharyngeal and upper oesophageal phases of swallowing) is subserved by skeletal muscles. These are driven rhythmically and automatically by CPGs within the pons and medulla. And, just like components of the autonomic nervous system, respiratory (and swallowing) muscles can be engaged volitionally. Moreover, central respiratory control has for a long time been considered in parallel with central cardiovascular control. But why is respiration special? Simply because it operates automatically, without conscious awareness? In other words, it operates autonomically and, like other elements of the ANS, it relies on sensory feedback, such as that provided by the peripheral and central chemoreceptors, to adjust its output. So, if respiration can be considered in this way, why can't we consider swallowing and locomotion in the same manner? I suggest that the term "autonomic nervous system" is too restrictive: it should not be limited to the classic branches of the ANS - the sympathetic, parasympathetic and enteric components - but should be defined as any system that utilises a CPG.

TOPIC 11. Emerging concepts and novel perspectives in autonomic neuroscience

O.38 Lineage And Organ Signals Sequentially Build Organ Intrinsic Nervous Systems

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Organ intrinsic nervous systems (OINSs) are critical components of the body-brain axis, coordinating visceral organ function with systemic physiological control. Despite their importance, how these distinct neural architectures arise from a common neural crest cell (NCC) origin has remained unclear. Here, we present a systems-level, cross-organ analysis of OINS development, integrating lineage tracing, 3D imaging, single-cell transcriptomics, and genetic perturbations across heart, pancreas, intestine, and lungs. We show that differences in NCC migratory trajectories prefigure the spatial architecture of OINSs, laying the foundation for organ-specific patterning. In contrast, molecular identity emerges largely in response to local environments, indicating that extrinsic cues play a major instructive role. Using in vitro co-cultures, we demonstrate that organ-derived cues reprogram intrinsic neurons toward organ-specific transcriptional profiles and direct neuronal differentiation, with extracellular matrix (ECM) contact as a central mediator. In vivo, ECM-integrin signaling supports intrinsic cardiac neuron neurogenesis, while ECM crosslinking stabilizes their stereotyped ganglionic organization. Together, these findings reveal that OINS diversity arises through a dual logic: lineage programs prefigure spatial frameworks, while organ-specific cues instruct final molecular identities and architectural precision. This work establishes a conceptual paradigm for how organs actively build their nervous systems, illuminating principles underlying body-brain integration (Nature, accepted).

TOPIC 07. Molecular and systems-level mapping of autonomic circuits and brain–body integration

O.39 The Interoceptive/homeostatic Reset System: A Neurological Model For Therapeutic Grounding In Dissociation And Trauma-related Dysregulation

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Certain chemicals that are absorbed, inhaled, or applied to the skin can exert physiological as well as psychological effects that may be exploited therapeutically. For example, pungent substances such as pickle juice or irritant vapours from ammonia salts can be used by therapists working with patients presenting with complex trauma and functional/dissociative seizures to help them reconnect with their body and sense of self. This process is known as grounding. We propose here a neurobiological model of the therapeutic effects of grounding stimuli that may be useful to clinicians and their patients.

Most grounding stimuli appear to be transduced into neural signals by Transient Receptor Potential (TRP) channels located throughout the body, including the viscera, mucosal membranes, and skin. Upon entering the central nervous system, these signals undergo an initial relay before ascending the neuraxis to target integrative centres in the brainstem and forebrain, ultimately terminating in the insular cortex and limbic lobe. Some of these signals are consciously perceived whereas others are not; however, all contribute to a representation of bodily state known as interoception. This ascending pathway corresponds to the interoceptive sensory pathway proposed by Craig (1).

Grounding stimuli also share the capacity to challenge homeostasis with the production of immediate autonomic, behavioural, and arousal responses to restore physiological balance. It is therefore not surprising that many of the integrative centres targeted by the interoceptive pathway are components of the descending central autonomic system and, more broadly, of the emotional motor system proposed by Holstege (2). Homeostatic resetting extends into the limbic system, where balance can be restored among structures such as the amygdala, anterior cingulate cortex, and prefrontal cortex during overmodulated or undermodulated pathological states.

In summary, the interoceptive/homeostatic reset model proposes that the therapeutic effects of grounding stimuli such as pickle juice and ammonia salts, arise from their ability to activate the interoceptive sensory pathway and trigger rapid homeostatic reset responses, thereby facilitating reconnection with bodily state and external reality.

1. Craig AD. 2002. Nat Rev Neurosci 8: 655-66

18TH Symposium - TRANSCRIPTOMIC SIGNATURES OF AUTONOMIC GANGLIA IN HEALTH AND DISEASE

TOPIC 07. Molecular and systems-level mapping of autonomic circuits and brain–body integration

S.67 Defining A Glia-mediated Barrier In The Peripheral Nervous System

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Satellite glia are the predominant glial cell type in sympathetic and sensory ganglia in the peripheral nervous system and specifically contact neuronal cell bodies. The intimate association of satellite glial cells (SGCs) with neuronal cell bodies positions these glia as critical regulators of neuronal homeostasis, architecture, and function. Despite their abundance and close association with neurons, SGCs remain among the most under-studied cell types in the nervous system. Using single-cell RNA sequencing, we provided the first evidence of the remarkable molecular diversity of SGCs (Mapps et al., Cell Reports 2022). We identified five distinct subtypes, defined by new and unique cohorts of molecular markers in sympathetic and sensory ganglia. Importantly, we found molecular differences between sympathetic and sensory SGCs, suggesting that SGCs are transcriptionally tuned to their resident ganglia. Through genetic ablation studies in mice, we demonstrated that SGCs are critical for restricting neuronal activity (Mapps et al., eLife 2022).

In ongoing work, we are defining ganglion-specific differences in SGC organization that influence their ability to shield neurons from the surrounding microenvironment in sympathetic versus sensory ganglia. Our findings suggest that sympathetic SGCs form a more effective protective barrier against systemic factors than sensory SGCs. We are currently testing the hypothesis that differences in barrier properties between sympathetic and sensory SGCs underlie the differential susceptibility of neurons to bortezomib, a chemotherapeutic agent that induces peripheral neuropathy. By defining structural and molecular differences in a glial barrier that regulates traffic between peripheral neurons and the circulation, our work establishes a new conceptual framework for understanding why certain neurons are more susceptible to circulating neurotoxins and pathogens and opens new therapeutic avenues to protect peripheral neurons from systemic insults.

S.68 Molecular heterogeneity and sensory coding in visceral afferent and parasympathetic pathways

Tongtong Wang (California Institute of Technology, USA)

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.261 - Spatial Transcriptomic Mapping Of The Intrinsic Cardiac Nervous System

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Introduction: The intrinsic cardiac nervous system is comprised of a network of ganglionated plexuses (GPs) embedded in epicardial fat pads on the heart. Neurochemical coding of the intrinsic cardiac nervous system has mostly been performed at the protein level using immunohistochemical techniques. The objective of this study was to develop a 3D spatial transcriptomic map of intrinsic cardiac ganglia in the right atrial GP (RAGP) and further characterize neuroanatomical connections between the RAGP and sinoatrial nodal region.

Methods: To identify neurons projecting to the SAN, retrograde neuronal tracer FastBlue was injected into the sinoatrial node in vivo in four pigs. Three weeks later, hearts were collected, and FastBlue-labeled and unlabeled neurons were collected using laser capture microdissection for gene expression profiling using high throughput PCR and RNA sequencing. Images were obtained during sectioning to generate a 3D map.

Results: Four hundred and five neurons across four pigs were evaluated using high throughput qRT-PCR to evaluate the repertoire of neurotransmitter receptors and ion channels. Notably, there was a heterogeneity in adrenergic, cholinergic, and peptidergic receptor profiles. Genes encoding hyperpolarization-activated cyclic nucleotide-gated (HCN) channels HCN2, which is found in nociceptive neurons and mediates Ih, and HCN4, which also mediates Ih in neurons as well as If in pacemaker cells of the hearts, are expressed in RAGP neurons. Spatial tracking and RNA sequencing of 90 neuronal samples using a 3D representation of the RAGP identified a distinct composition of neurons. Of note, significant co-expression of cholinergic and adrenergic genes was identified.

Conclusions: Gene expression profiling of intrinsic cardiac neurons uncovers a phenotypic diversity not ascertainable by immunohistochemical methods. Co-expression of cholinergic and catecholaminergic genes was found in the RAGP, distinct from immunolabeling experiments, raising the possibility of plasticity with effects on parasympathetic control of sinoatrial nodal function.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.70 - Spatial Transcriptomic Mapping Of Autonomic Circuits In Cardiovascular Pathology

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The sympathetic nervous system is a central regulator of cardiovascular function and systemic stress responses. Dysregulation of sympathetic activity is a hallmark of multiple cardiac pathologies, including chronic heart disease and stress-induced cardiomyopathies such as Takotsubo syndrome. While immune-sympathetic interactions have been implicated in peripheral organs, the cellular architecture and molecular mechanisms driving sympathetic dysfunction remain poorly understood.

Here, we apply spatial transcriptomic and single-nucleus approaches to map disease-associated remodeling of autonomic circuits in human and murine models of cardiovascular pathology. Spatially resolved and integrative transcriptomic analyses reveal a macrophage-centered inflammatory program characterized by increased cytokine signaling and adhesion molecule expression, consistent with active immune recruitment and local circuit reorganization.

Within the superior cervical ganglion (SCG), we identify pronounced structural remodeling accompanied by marked accumulation of inflammatory macrophages and altered neuronal states. Functionally, targeted depletion of macrophages in the SCG attenuates ganglionic remodeling, dampens pathological sympathetic signaling, and mitigates cardiac disease progression and associated comorbidities. Together, these findings establish sympathetic ganglia as spatially organized immunomodulatory hubs and reveal neuroimmune crosstalk within the sympathetic nervous system as a previously underappreciated and therapeutically actionable axis in cardiac disease.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.40 P2X3 Receptor Expression In The Human Stellate Ganglion

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Introduction: Cardiovascular diseases are characterised by sympathetic nerve overactivity, which contributes to end-organ damage, morbidity and mortality. Stellate ganglia provide the primary sympathetic innervation to the heart. We have recently shown upregulation of P2X3 purinergic receptors (P2X3R) in the stellate ganglia of Spontaneously Hypertensive (SHR) compared to Wistar rats [1]. Excitingly, we demonstrated that P2X3R contribute to cardiac regulation and that inhibiting P2X3R shows great potential as a novel and effective treatment for cardiac arrhythmias in rats [1]. We aimed to investigate whether 1) P2X3R are expressed in human stellate ganglia, 2) P2X3R expression correlates with heart disease, and 3) sex differences are evident in stellate ganglion P2X3R expression.

Methods: Human stellate ganglia were collected from donors to the University of Auckland (n=21). Immunofluorescent analysis was used to determine the expression of P2X3R, and the extent of co-localisation within tyrosine-hydroxylase (TH) positive sympathetic neurons.

Results: P2X3R protein expression is confirmed in human stellate ganglia, and co-localises within sympathetic neurons. Preliminary analysis suggests higher P2X3R expression in stellate ganglia from patients with heart disease compared to those without. Furthermore, analysis suggests more sympathetic neurons within the stellate ganglia in heart disease, which may indicate a novel mechanism of sympathetic overactivity. Analysis is ongoing to determine whether sex differences in stellate ganglia may contribute to differential disease profiles.

Conclusion: As the first evidence of P2X3R expression and activity in human stellate ganglia, these data provide vital support for the clinical translation of P2X3R inhibitors to treat cardiac arrhythmias in men and women.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.41 Pathogenic CHRNA3 Gene Variants Demonstrates Variable Clinical Expression In Familial Autonomic Ganglionopathy

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Introduction: Our team previously reported a novel genetic disease that affected 3 individuals from 2 unrelated families who presented with severe neurogenic OH, miosis with peripheral iris thinning, constipation, and urinary retention. These patients had rare pathological variants in the CHRNA3 gene that were predicted to destabilize the nicotinic AChR pentameric complex, responsible for ganglionic transmission of sympathetic and parasympathetic nerves.

Methods: Since the initial report, we identified two additional patients from two different families, who presented primarily with impaired gastrointestinal motility, neurogenic bladder, orthostatic intolerance and impaired pupillary constriction. Autonomic function tests, norepinephrine (NE) levels and pyridostigmine challenge were performed.

Results: Two affected individuals: a 19-year-old German woman (III-4, case reported), a 10-year-old girl (IV-5), from unrelated families, were identified. Whole-exome sequencing identified a compound heterozygosity, comprising a frameshift variant c.907_908delCT (p.Leu303Aspfs115) and a maternally inherited deletion of CHRNA3 exons 5–6 in case III-4. The other patient (IV-5) was homozygous for c.907_908delCT (p.Leu303Aspfs115). Visceral symptoms were prominent in both cases, including constipation, enlarged colon, impaired bladder emptying with urosepsis requiring vesicostomy in III-4 and self-catheterization in IV-5. Orthostatic intolerance and hypoglycemia were disabling in III-4, whereas IV-5 endorsed minor symptoms. Both had neurogenic OH and low NE levels, but IV-5 had a normal compensatory increase in HR and preserved sinus arrhythmia, suggesting preserved cardiovagal function. The pyridostigmine challenge was not effective in III-4, whereas it significantly improved visceral and orthostatic symptoms in IV-5.

Conclusion: We report two additional families with familial autonomic ganglionopathy and different clinical expressions. The phenotype may reflect variable penetrance of pathogenic CHRNA3 variants. Considering the high-carrier frequency of the CHRNA3 frameshift variant c.907_908delCT, the CHRNA mutation should be considered in patients with early-onset pan-dysautonomia with visceral symptoms, even in the absence of orthostatic intolerance.

19TH Symposium - ALTERED REGULATION OF SYMPATHETIC NERVE ACTIVITY IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.71 Control Of Muscle Sympathetic Nerve Activity During Rest And Dynamic Exercise In HFpEF

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Introduction: Heart failure (HF) is a principal cause of debilitating symptoms, hospitalizations, and premature death. HF with preserved ejection fraction (HFpEF) accounts for approximately half of all cases and patients are characterized by disabling exercise intolerance, yet underlying pathophysiology remains incompletely understood. Sympathetic nervous system activation at rest and during exercise is well-recognized as an important mechanism of disease progression and functional limitation in HF with reduced ejection fraction (HFrEF), but, at present, whether similar sympathetic excitation is extant in HFpEF, independent of the many comorbidities that afflict such patients, and limit their exercise capacity, is unknown. Methods: Using microneurography, we recorded multi-unit muscle sympathetic nerve activity (MSNA), heart rate (HR), and blood pressure (BP) at rest and during exercise in patients with HFpEF, controls matched as closely as possible for age, sex, resting BP, medication use, and the presence of major comorbidities accompanying patients with HFpEF, as well as unmedicated, age- and sex-matched healthy controls. All participants completed baseline, isometric and rhythmic handgrip, and 1-leg dynamic cycling exercise protocols during which MSNA, HR, and BP were measured continuously. Exercise capacity was assessed in all by peak oxygen uptake (VO2peak). Results: Resting MSNA was higher and VO2peak lower in HFpEF versus comorbidity-matched controls and healthy controls. During isometric and rhythmic handgrip exercise, MSNA increased in all groups, resulting in higher absolute MSNA in patients with HFpEF. During 1-leg cycling exercise, MSNA decreased during mild and moderate cycling in healthy controls, was unchanged during mild and moderate cycling in comorbidity-matched controls, yet increased, ‘paradoxically’, in patients with HFpEF during both mild and moderate cycling. The magnitude of exercise-induced muscle sympathetic excitation during cycling related inversely to VO2peak in HFpEF patients, but not in either control group. Conclusion: In patients with HFpEF, MSNA is augmented at rest and during exercise, compared with both comorbidity-matched controls and healthy individuals. These data are consistent with the concept of a peripheral, neurogenic vasoconstrictor limit on exercise in HFpEF, as seen previously in patients with HFrEF. Importantly, these disturbances appear intrinsic to HFpEF, rather than consequences of the several comorbidities present in such patients.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.72 Sex Differences In Sympathetic Neural Control In Hfpef (symposium)

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Heart failure with preserved ejection fraction (HFpEF) is more common in older females than older males, and female patients often report poorer quality of life. These sex differences may reflect variations in sympathetic neural control and humoral responses to obesity, a major HFpEF risk factor affecting more than 80% of U.S. patients. Obesity-related HFpEF has been associated with systemic inflammation, sympathetic activation, sodium retention, and plasma volume expansion. This presentation compares sympathetic neural activity, inflammatory biomarkers, renal-adrenal hormones, and plasma and blood volume in male and female patients with HFpEF, as well as in non-HFpEF controls. The impact of weight loss on neural and humoral adaptations in HFpEF is also discussed. Evidence indicates that obesity, inflammation, and sympathetic neural activity are linked differently by sex, with female patients demonstrating greater obesity-related sympathetic activation than male patients. These findings suggest that obesity-driven inflammation is a key contributor to HFpEF in females, whereas volume expansion and other mechanisms may be more important in males.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.73 Control Of Cardiac Sympathetic Nerve Activity In Ovine Hypertensive Heart Failure With Preserved Ejection Fraction

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Introduction: The sympathetic nervous system (SNS) plays a crucial role in regulating cardiovascular function, particularly during changes in physiological demand. However, the role of the cardiac SNS in heart failure with preserved ejection fraction (HFpEF), a syndrome characterised by impaired cardiovascular reserve and exercise intolerance, has not been thoroughly investigated. Although current evidence suggests that cardiac sympathetic overactivity is not a prominent feature of HFpEF, this has not been directly tested. Accordingly, studies were performed to determine whether cardiac sympathetic nerve activity (SNA) is dysregulated in HFpEF at rest and during physiological challenges such as exercise and blood volume expanded (congested) states.

Methods: Since direct recordings of cardiac SNA are not feasible in humans, a large animal model of HFpEF was developed in older female sheep using chronic two-kidney, one-clip hypertension, reflecting key clinical risk factors. Cardiac structure and function were assessed alongside directly measured haemodynamic responses at rest and during graded exercise testing. Cardiac SNA was directly recorded in conscious animals, and the effects of pharmacological inhibition of cardiac SNA using a β-blocker during exercise, as well as responses to acute blood volume expansion, were evaluated.

Results: HFpEF sheep exhibited hallmark features of the syndrome, including diastolic dysfunction, cardiac hypertrophy, preserved systolic function, and impaired cardiac and extracardiac exercise haemodynamics. Resting cardiac SNA was not elevated. However, β-blockade produced differential and detrimental changes in exercise haemodynamics in HFpEF compared with non-HFpEF sheep, indicating greater reliance on cardiac SNA during exercise. During acute blood volume expansion, cardiac SNA decreased, with no difference in response between HFpEF and non-HFpEF animals.

Conclusion: These studies provide the first in vivo conscious recordings of cardiac SNA in HFpEF, demonstrating that both resting activity and its reflex responses remain largely intact, in contrast to the marked SNS dysregulation observed in heart failure with reduced ejection fraction. These findings support recent clinical recommendations to avoid routine use of sympathoinhibitors such as β-blockers in HFpEF in the absence of clear indications. Further work is required to elucidate the role of non-cardiac SNS activity in HFpEF pathophysiology and the role of the SNS across specific HFpEF phenotypes.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.42 Restoring Cardiorespiratory Coupling To Improve Exercise Capacity In Hypertensive HFpEF Sheep

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Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent global health problem characterized by impaired exercise capacity, elevated ventricular stiffness, and limited therapeutic options. An under-explored feature of HFpEF physiology is the loss of respiratory heart rate variability (RespHRV), the natural coupling of heart rate to breathing. In parallel, depressed myocardial energy metabolism is central to HFpEF pathophysiology [1].

Given the reverse-remodelling of the heart in HFreducedEF following RespHRV pacing [2,3], we hypothesized that restoring RespHRV in HFpEF would increase cardiac efficiency, cardiac output reserve and exercise performance in HFpEF. Studies were conducted in a conscious ovine (ewe) model of hypertensive HFpEF that replicates the impaired exercise hemodynamics observed clinically [4]. Following one week of baseline measurements, animals underwent two weeks of RespHRV pacing. Exercise capacity was assessed using serial treadmill testing and the increase in cardiac output from rest to peak exercise was determined.

Preliminary data (n=2) demonstrated that RespHRV pacing increased resting cardiac output and enhanced exercise hemodynamics, with an increase in peak cardiac output. Before pacing, cardiac output increased by 7.1±0.9 L/min during exercise. This increased to 10±0.9 L/min after 2 week of RespHRV pacing, indicating a progressively greater capacity of heart pump function during exercise.

Future direction: The effect of RespHRV pacing will be compared with monotonically paced and non-paced control groups of HFpEF sheep. Cardiac function will be further characterized using echocardiography and pressure-volume loop analysis, alongside metabolic profiling of myocardial tissue to assess changes in substrate utilization and mitochondrial structure. In conclusion, we provide the first evidence (albeit preliminary) that RespHRV pacing improves cardiac pump function in HFpEF offering a much-needed novel therapeutic treatment for patients.

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TOPIC 01. Cardiovascular autonomic regulation in health and disease

O. 43 Old Drug, New Purpose – The Effects Of Tadalafil On Carotid Body Activity In Heart Failure

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Introduction: Carotid bodies (CBs), the main peripheral oxygen sensors, are one of the drivers of sympathetic overdrive in heart failure (HF). An increase in CB activity in HF has been attributed to changes in mitochondrial function, elevated oxidative stress and a decrease in cGMP signalling. Acutely, increasing cGMP signalling resulted in a decrease in type I cells activity in HF. We hypothesised that normalising cGMP levels in HF by inhibiting phosphodiesterase 5, and therefore the breakdown of cGMP, with chronic tadalafil treatment could have beneficial effects on CB function. We aimed to characterise tadalafil effects on CB hypoxic ventilatory response (HVR), mitochondrial function and ROS production.

Methods: HF was induced by rapid pacing of the right ventricle of female Welsh mountain sheep. After 4 weeks tachypacing, a subset of HF animals received tadalafil (20 mg daily) for 3 weeks with continued tachypacing. All treated animals underwent a spirometry assessment to measure HVR and therefore CB hypoxic sensitivity at baseline, week 4 and after tadalafil treatment. Mitochondria were isolated from CBs to perform high resolution respirometry to measure mitochondrial oxygen consumption and H2O2 production by using substrate-uncoupler-inhibitor titration protocols, and kinetics of mitochondrial oxygen affinity.

Results: An increase in HVR was observed in 7 out of 9 HF animals ($p = 0.008$). Treated animals had elevated HVR at 4 weeks ($p = 0.026$), which was then normalised with tadalafil ($p = 0.006$). An increase in HVR was accompanied by a decrease in complex IV oxygen affinity in the HF group ($p = 0.037$), which was not normalised in the tadalafil cohort. The mitochondrial respiration or ROS production were unaffected by HF or tadalafil treatment.

Conclusion: In summary, tadalafil had beneficial effects on CB activity in HF. While mitochondrial respiration was unchanged in HF or following tadalafil treatment, a decrease in oxygen affinity was observed in HF. The CB hypoxic responsiveness was normalised with tadalafil, although this does not appear to normalise the mitochondrial oxygen affinity. Our data highlight that the beneficial effects of phosphodiesterase inhibitors can be observed beyond the myocardium and vasculature.

20TH Symposium - INTERPLAY OF INTEROCEPTION AND THE AUTONOMIC NERVOUS SYSTEM IN HEALTH AND DISEASE

S.74 The new science of interoception and its relationship with the autonomic nervous system

Lucia Ricciardi (George's University of London, UK)

S.75 Measuring brain-heart and other organs interactions

Diego Candia-Riveira (Sorbonne Université, France)

S.76 Clinical implications of interoceptive-autonomic changes

Diogo Carneiro (ULS Coimbra, Portugal)

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.44 A Study Of Interrelationship Between Heart Rate Variability, Anthropometric Profiles, Physical Fitness, And Happiness.

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Background: The autonomic nervous system (ANS) is key player in regulating emotional well-being and physical resilience. Happiness is a construct that is considered as physiologically relevant. The interrelationship of happiness with autonomic tone, body composition, and physical fitness not understood well. This study investigated the interplay between happiness, cardiac autonomic function (heart rate variability, HRV), somatotype, and exercise response in apparently healthy adults.

Methods: After due approval from institutional ethics committee and informed consent, 115 participants (91 males, 19 females; mean age 30.1 ± 6.2 years) were recruited. Participants underwent comprehensive evaluations. Somatotype was determined using Heath-Carter equations from standardised eight measurements. Physical fitness was assessed via the modified Harvard Step Test. Short-term HRV (5-min resting ECG, lead II) was analysed. Oxford Happiness Questionnaire was used for assessing happiness. Pearson correlations, independent-samples t-tests, and one-way ANOVA were employed.

Results: Mean happiness (OHI) score was 4.52 ± 0.62. Happiness correlated positively with resting heart rate ($r = 0.323$, $p < 0.001$) and RMSSD ($r = 0.275$, $p < 0.001$), and negatively with HF nu ($r = -0.234$, $p = 0.002$), suggesting a sympathovagal signature associated with greater well-being. Participants showing poor physical fitness and delayed post-exercise recovery on the Harvard step test exhibited high sympathetic dominance (elevated resting Mean HR and LF/HF ratios). Exercise duration ($r = 0.178$, $p = 0.020$) and peak HR response ($r = 0.163$, $p = 0.034$) independently correlated with happiness. Somatotype significantly modulated happiness scores (ANOVA $F = 3.08$, $p = 0.029$): endomorphic individuals reported higher happiness (4.59 ± 0.63) compared to ectomorphic (4.07 ± 0.54) and ecto-endomorphic (3.90 ± 0.58) types. Females demonstrated markedly higher HF nu than males (51.0 vs. 31.2 n.u.; $p = 0.002$), indicating greater vagal tone.

Conclusion: These findings demonstrate a clear link between happiness and enhanced vagal flexibility, physical fitness, and somatotype. Greater exercise capacity independently supports happiness. This suggests body built and cardiac autonomic regulation are co-determinants of well-being and support a biopsychophysiological model of happiness and highlight the relevance of autonomic neuroscience in understanding emotional health.

TOPIC 08. Autonomic control of metabolism and energy homeostasis

O.45 The Liver Modulates Afferent Hepatic Vagal Nerve Activity To Affect Parasympathetic And Sympathetic Tone At Skeletal Muscle And Glucose Homeostasis.

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Introduction: Fatty liver is associated with worsened hypertension, insulin resistance, and hyperinsulinemia. Vascular perfusion of skeletal muscle is a robust regulator of skeletal muscle glucose clearance/insulin sensitivity and total blood volume. The insulin resistance and hyperinsulinemia in diet-induced obese mice can be prevented by surgically manipulating hepatic vagal nerve signaling or pharmacologically preventing liver GABA production. We hypothesize that the hepatic vagal nerve modulates skeletal muscle projecting vagal nerves to affect insulin sensitivity.

Methods: We performed a series of studies aimed at understanding the role of the hepatic vagal nerve in regulating efferent sympathetic and parasympathetic nervous system activity at skeletal muscle and insulin sensitivity. These included acute bath application of the GABAA agonist, muscimol, onto the hepatic vagal nerve, pharmacologically limiting liver GABA production, and using DREADDs (designer receptors exclusively activated by designer drugs) to acutely manipulate afferent hepatic vagal nerve activity.

Results: Pharmacologically inhibiting liver GABA production (EOS in drinking water 3g/L for 5 days) increased soleus cGMP concentration in diet-induced obese mice ($P = 0.05$). Bath application of muscimol (10 μM) onto the hepatic vagal nerve increases peroneal nerve activity in chow fed lean anesthetized mice. Acute inhibition of the hepatic vagal nerve in chow fed mice increases glucose stimulated serum insulin ($P = 0.02$) without affecting glucose tolerance, proposing that inhibition of the hepatic vagal nerves. In diet-induced obese mice (9 weeks on high fat diet) acute inhibition of the hepatic vagal nerve worsens oral glucose tolerance, while acute activation of the hepatic vagal nerve limits GSIS.

Conclusion: The hepatic vagal nerve regulates efferent peripheral nervous system at skeletal muscle to affect glucose homeostasis.

TOPIC 09. Gastrointestinal and visceral autonomic regulation

O.46 Sensory Circuits For The Recruitment Of Swallow.

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The oral cavity is innervated by multiple cranial sensory nerves, including branches of the trigeminal, facial, glossopharyngeal, and vagus. These afferents arise from diverse neuronal populations that encode both somatosensory and viscerosensory information. Sensory input from the oral cavity plays a critical role in triggering swallowing, yet the specific cell types and mechanisms underlying this essential sensory perception remain poorly understood. In this study, we systematically map the innervation of the oral cavity, defining its genetic sensory neuron subtypes, their functional properties, and their interactions with central neurons that organize the swallowing motor pattern.

21ST Symposium - INFLAMED CIRCUITS: BRAIN IMMUNE CELLS SHAPING CARDIOVASCULAR OUTCOMES

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.77 The Effects Of Exercise Training On Blood Pressure, Microglia Activation And BBB Function

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Blood-brain barrier (BBB) dysfunction is a hallmark of hypertension and neuroinflammation. Microglia regulate BBB integrity via pro-inflammatory cytokines, particularly tumor necrosis factor-α (TNFα), which degrade basement membrane and tight junction proteins of cerebral vessels. Exercise training attenuates BBB leakage, but the underlying mechanisms remain poorly defined. Spontaneously hypertensive rats (SHR) and normotensive controls were assessed for microglial activation and TNFα production by flow cytometry in trained and sedentary groups. In a separate SHR cohort, blood pressure was continuously monitored by telemetry in sedentary, trained, and TNFα-blocked animals. BBB permeability was evaluated using cocktail of fluorescent tracers. SHR showed increased microglial activation and TNFα production in the hypothalamus and brainstem, both reversed by exercise. TNFα blockade reduced BBB leakage in the paraventricular nucleus, nucleus of the solitary tract, and rostral ventrolateral medulla, and lowered blood pressure, similar effects elicited by the exercise training. Exercise mitigates BBB disruption in hypertension by suppressing microglial activation and TNFα signaling. Pharmacological TNF-α blockade reproduces these effects, highlighting microglial modulation as a therapeutic target for hypertension-induced neurovascular dysfunction.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.78 Inflammation In The Area Postrema After Cardiopulmonary Bypass In Sheep

Lisa Hong (1) - Anton Trask-marino (2) - Angela Connelly (2) - Emily Hadzajlic (1) - Taku Furukawa (2) - Alemayehu Jufar (2) - Clive May (2) - Yugeesh Lankadeva (2) - Song Yao (1) - Lindsea Booth (2)

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Introduction: Over two million cardiac procedures are performed annually worldwide that rely on cardiopulmonary bypass (CPB), often serving as a last resort surgery for patients with heart failure. Although, this is a lifesaving intervention, approximately 30% of patients experience a diminished quality of life in the years that follow due to symptoms related to autonomic dysfunction, such as bradycardia, tachycardia and postural hypotension. Neuroinflammation is hypothesised to contribute to the cognitive deficits experienced after CPB; however, the level of neuroinflammation in the autonomic control centres of the brainstem has not been investigated.

Methods: Healthy Merino ewes (n=8) and ewes with myocardial infarction-induced heart failure (n=8) underwent two hours of CPB followed by a 48 hour recovery period. Blood pressure and heart rate were measured before, during and in the recovery period following CPB and were analysed to determine changes in heart rate and blood pressure variability. At the end of 48 hours, ewes were killed with an overdose of pentobarbitone, and brain tissue was collected for immunohistochemical analysis. Morphological changes in microglia and astrocytes were determined across key autonomic centres, including the area postrema, nucleus of solitary tract and dorsal motor nucleus of vagus.

Results: Heart failure was associated with a significant drop in heart rate variability. Preliminary findings show that the highest level of microglial activation occurs after CPB in sheep with heart failure, in the area postrema, a circumventricular organ not protected by the blood-brain barrier. Morphological changes in microglia and astrocytes were more subtle in the nucleus of solitary tract.

Conclusions: Exaggerated inflammation in important autonomic centres may underlie some of the autonomic dysfunction experienced by patients who undergo CPB. Future studies should determine whether reducing inflammation reduces autonomic dysfunction after CPB.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

S.79 Il-1b Mediated Increases In Blood Pressure In The Area Postrema Via Direct Projections To The Rostral Ventrolateral Medulla

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Background: The area postrema (AP) is a brain region that lacks a blood-brain barrier, allowing blood-borne factors to access the brain. Because the AP is connected to multiple regions that regulate blood pressure, we hypothesised that blood-borne inflammatory mediators such as interleukin-1 beta (IL-1β) could contribute to the development of hypertension. Supporting this hypothesis, plasma IL-1β is increased in hypertensive patients (Dalekos et al., 1997, J Lab Clin Med, 129: 300-8), and IL-1β receptors are abundantly expressed in the AP.

Aims: To test whether IL-1β acting at the AP increases blood pressure and renal sympathetic nerve activity (RSNA) in rats.

Methods: In anaesthetised rats, blood pressure and RSNA were recorded following microinjection of IL-1β into the AP at two doses (10 ng and 25 ng). To determine specificity, specific IL-1 receptor blocking antibodies (IL-1Ra) were injected into the AP prior to a 25 ng IL-1β injection. Responses were compared with saline controls and analysed statistically (see Results).

Results: Microinjection of 25 ng IL-1β produced a significant increase in systolic blood pressure and heart rate compared with saline controls ($p < 0.01$; Mann-Whitney test). The increases were: systolic blood pressure 19.6 ± 3.6 mmHg versus saline 5.47 ± 1.58 mmHg, and heart rate 55 ± 10 bpm versus saline 12 ± 6 bpm. Pre-treatment with IL-1Ra attenuated the IL-1β-induced responses, producing effects comparable with saline controls. IL-1β also increased RSNA (137% ± 43%). Immunohistochemistry showed that IL-1β injection induced Fos activation in the AP.

Conclusions: IL-1β application to the area postrema activates local neurons and produces increases in blood pressure, heart rate and RSNA. These findings provide new insight into central actions of IL-1β and indicate that IL-1β signalling in the AP may be a potential target for future antihypertensive therapies.

TOPIC 04. Neuroimmune communication and neural control of immune responses

S.80 Neuroimmune Crosstalk in Hypertension: RORγt as a Mediator of Angiotensin II-induced Microglial Activation and BBB Breakdown

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Interleukin (IL)-17A is a proinflammatory cytokine that contributes to neuroinflammation, sympathetic excitation, and cardiovascular dysfunction in hypertension. Retinoid-related orphan receptor γ t (ROR γ t), the master transcription factor for T helper 17 cell differentiation, regulates IL-17A production. We previously demonstrated that IL-17A promotes blood-brain barrier (BBB) disruption, microglial activation, and sympathetic overactivity in angiotensin II (ANG II)-induced hypertension. The present study investigated whether inhibition of ROR γ t could attenuate neuroinflammation and sympathetic activation by reducing IL-17A production and preserving BBB integrity. Rats were subjected to chronic ANG II infusion and treated with either the ROR γ t inhibitor digoxin or vehicle. ANG II infusion increased IL-17A levels in both the circulation and central nervous system, accompanied by elevated blood pressure and sympathetic tone. These effects were markedly attenuated by ROR γ t inhibition. In the hypothalamic paraventricular nucleus (PVN), a key autonomic regulatory center, ANG II induced BBB dysfunction characterized by enhanced endothelial transcytosis, reduced expression of the BBB-protective transporter Mfsd2a, degradation of tight junction proteins, and increased BBB permeability. ROR γ t inhibition largely reversed these alterations and preserved BBB integrity. In addition, ANG II promoted microglial activation and increased expression of proinflammatory cytokines within the PVN, whereas digoxin treatment attenuated these neuroinflammatory responses. These findings demonstrate that inhibition of ROR γ t mitigates ANG II-induced hypertension and sympathetic excitation, likely through suppression of IL-17A production, preservation of BBB integrity, and attenuation of microglial activation and neuroinflammation within autonomic brain regions. The ROR γ t–IL-17A signaling pathway may therefore represent a promising therapeutic target for neurogenic hypertension.

TOPIC 01. Cardiovascular autonomic regulation in health and disease

O.47 Which Antibodies Are We Still Missing? 15 Years Later And Still – When In Doubt – Glucocorticoids To The Rescue! A Case Of Seronegative Autoimmune Autonomic Ganglionopathy

Antun Rudolf Pavelic [1] **- Stephanie Hödl** [2] **- Walter Struhal** [1]

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Fifteen years ago, Struhal et al. published a case of acute pandysautonomia healed by high-dose prednisolone therapy. In February 2026, a 38-year-old male was referred to our neurology department with persistent, progressive pupillotonia (L>R), urinary retention, constipation, anhidrosis, sicca syndrome, xerostomia, sleeping disturbance, and orthostatic intolerance with dizziness. Symptoms began January 3, 2026, after a self-limited diarrhea 4 days earlier. The patient presented initially at an ophthalmology practice due to blurry vision. Sjörgren's Syndrome was suspected and he was admitted to the rheumatology department at a nearby Hospital. He was seronegative for Sjörgren's Syndrome and referred to the University Hospital. A complete neurological work-up, including MRI and full spine MRI was conducted. Further investigations included a thoracoabdominal CT (to exclude neoplastic processes), lumbar puncture (screening for meningitis causes, neuroborreliosis, ganglioside-, onconeuronal-, autoimmune- and ganglionic-antibodies (Abs)), ENG incl. sympathetic skin response (SSR), multi-panel neuronal-Abs, and α-3-acetylcholine-recpetor-Abs. The COMPASS-31 score was 47 points. The CSF showed no abnormalities, α-3-Acetylcholine-recpetor-Abs were negative and the SSR showed no detectable responses in any extremity. Urological, ENT, surgical and internist consultations were conducted. A lip biopsy showed no clear evidence for Sjörgren's Syndrome. Tilt-table-testing (TTT) showed sympathetic and parasympathetic dysfunction with delayed orthostatic hypotension 14mins after tilt and 8 mins after standing. Ophthalmology confirmed the pupillotonia and the patient was diagnosed with seronegative autoimmune autonomic ganglionopathies (AAG). IVIG-treatment was started but led to aseptic meningitis; while symptomatic therapy minimally improved the patient's condition. Off-label treatment with 1000mg Prednisolone was administered over 5 days (with tapering afterwards) which led to almost immediate improvements. On follow-up, the patien's symptoms completely receded and TTT and SSR showed no signs of ANS dysfunction. This case exemplifies there is still potential remaining with respect to serological diagnostics in AAGs and the importance of regionally available AAG-Ab testing.

22ND Symposium - INTERDISCIPLINARY STUDIES OF NERVOUS SYSTEMS ASSOCIATED WITH THE GASTROINTESTINAL TRACT AND BEYOND

TOPIC 9. Gastrointestinal and visceral autonomic regulation

S.81 Neuronal Diversity And Connectivity In The Murine Gastrointestinal Tract.

Ulrika Marklund (1)

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The enteric nervous system (ENS) is organized into irregular ganglia composed of diverse and intermingled neuronal populations that extend throughout the gastrointestinal tract. Our laboratory seeks to define the cellular composition of the ENS at both molecular and circuit levels and to uncover how this diversity emerges during embryonic development. To this end, we have characterized the ENS of the mouse gastrointestinal tract across embryonic and juvenile stages using single-cell RNA sequencing, histochemical approaches, and analyses of mutant and transgenic mouse models. Within the small intestine, we identified 12 myenteric neuron classes and 3 submucosal plexus classes. Using class-specific Cre-driver mice, we are now systematically mapping the morphology, innervation patterns, and connectivity of each neuronal type. We are particularly interested in enteric interneurons, which still remain poorly understood. Our work has so far identified an excitatory interneuron subtype with highly selective connectivity, whereas another inhibitory interneuron type appear to establish more promiscuous connections across all neuronal classes. To further define these circuit architectures, we have implemented anterograde synaptic tracing and super-resolution microscopy. During the development, we have shown that the neuronal identities are shaped through a stepwise diversification process in which progenitor cells first undergo a binary fate decision, followed by additional diversification at postmitotic stages in both the myenteric and submucosal plexuses. Based on these findings and more recent comprehensive epigenetic and sequencing data, we propose a unified developmental framework for enteric neuron specification across the gut wall, in which temporal emergence and binary fate decisions together determine neuronal identity. Overall, by combining developmental, connectivity, and functional analyses at neuron-type resolution, we hope to resolve the core essence of “what the ENS is”, that could be of relevance for the rest of the peripheral nervous system and neuronal interconnectivity between organs.

TOPIC 9. Gastrointestinal and visceral autonomic regulation

S.82 Advances In Our Understanding Of Sensory Nerves In The Gut-brain Axis

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Compared with all other internal organs, the gastrointestinal tract is unique, because it contains not only its own intrinsic nervous system (the enteric nervous system, ENS) but also its own unique population of sensory neurons, known as intrinsic primary afferent neurons (IPANs). It has been very difficult to determine the functional role of IPANs in the gut wall until recent advances in neurogenetic techniques. RNA sequencing identified that the neuropeptide CGRP-β is highly expressed in IPANs. Therefore, we generated a transgenic mouse expressing inducible cre under the CGRP-β promotor. CGRP-β mice were crossbred with Ai9 mice to induce cre-driven expression of the fluorescent reporter protein, tdTomato. Reporter expression was identified in IPAN nerve cell bodies and numerous axons throughout the colonic myenteric plexus. This gave us a unique opportunity to identify and record from IPANs in intact neural networks. Calcium imaging of the ENS revealed that during cyclical colonic motor complexes (CMCs) IPANs generated time locked calcium transients at the same time as motor neurons and interneurons, forming a coordinated neural network. All calcium transients were blocked by hexamethonium (N=6). CGRP-β cre mice were crossbred with Ai32 mice to induce cre-driven expression of channelrhodopin-2. Blue light stimulation of the isolated colon wall evoked premature CMC contractions in mice expressing ChR2 in sensory neurons (N=5). The findings show that in contrast to intracellular electrophysiological recordings, intrinsic sensory neurons receive prominent fast synaptic inputs, in addition to behaving as sensory neurons. In the second part of this presentation, we demonstrate wireless optogenetic activation of extrinsic sensory nerve axons innervating the terminal large intestine of freely moving animals. Stimulation of spinal afferents (via Trpv1 promoter) in the terminal large intestine activated increased stress responses, whereas applying same stimuli to somatic afferents in the viscera activated writhing and abdominal pain (N=11). We demonstrate that wireless activation of the gut-brain axis induces distinct behavioural responses depending on the site of stimulation.

TOPIC 09. Gastrointestinal and visceral autonomic regulation

S.83 Volume-EM Analysis For Exploring New Comprehension In Gut Innervation Regulatory System

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Introduction: The gut regulation system comprises several components, including the enteric nervous system (ENS), interstitial cells of Cajal (ICC), platelet-derived growth factor receptor α + (PDGFR α +) cells, and the central nervous system. These elements form a complex network within the gastrointestinal wall through morphological interactions. Furthermore, each cellular function is determined by the organelle structure. In particular, ICC are characteristic pacemaker cells that possess specific structures for Calcium ion regulation. To accurately understand their functions, it is necessary to examine the ultrastructures of both intercellular and intracellular information, especially in three dimensions.

Methods: To accomplish this, novel volume electron microscopy (vEM) analysis was performed on mouse gastrointestinal tissues. vEM can provide a three-dimensional ultrastructure by acquiring serial EM images and stacking them. Specifically, focused ion beam/scanning electron microscopy (FIB/SEM) is ideal for these purposes because it allows the x, y, and z resolutions to be set sufficiently small to detect critical structures without losing information.

Results: Regarding the interaction among the nervous system and other elements, such as ICC, morphological categorization of nerves could be performed by examining their entire three-dimensional structures and vesicle types present in varicosities. Regarding cellular components, the formation of a specific ER structure facing the PM varied among smooth muscle cells, ICC, and PDGFR α + cells. These variations likely reflect the distinct functional roles of each cell type. In particular, the characteristic morphological unit called a “microdomain“ in ICC was analyzed precisely, and geometrical data, such as distances between ER and PM (100 nm on average), could be obtained. This microdomain structure is thought to regulate localized Calcium ion concentrations and is supposed to have unique pacemaker functions in ICC.

Conclusion: These novel morphological data obtained with FIB/SEM could provide new insights into the complicated innervation system in the gastrointestinal tract. Furthermore, cellular geometrical data could provide new clues for understanding cellular excitation mechanisms, which have traditionally been based on electrophysiological and pharmacological studies.

TOPIC 09. Gastrointestinal and visceral autonomic regulation

S.84 GLP-1 Released From The Gut Protects The Kidney Through The Nervous System

Shinji Tanaka (1)

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Since vagus nerve stimulation (VNS) was reported to exert potent anti-inflammatory effects, its clinical application has expanded, particularly in inflammatory and autoimmune diseases. Very recently, a phase 3 clinical trial reported that VNS is effective in patients with rheumatoid arthritis.

We previously reported that VNS attenuates acute kidney injury. In our recent study using optogenetics, we demonstrated that stimulation of either vagal efferent fibers or vagal afferent fibers is sufficient to attenuate kidney injury. We also identified the downstream pathway of vagal afferent fiber stimulation as follows: C1 neurons → sympathetic nervous system → splenic nerve → spleen → kidney.

Based on these findings, we are currently investigating a strategy to pharmacologically stimulate vagal afferent fibers. Allulose, a rare sugar, has been reported to induce GLP-1 release from intestinal L cells following oral administration and to suppress food intake via vagal afferent fibers. In this talk, I would like to discuss preliminary data regarding the mechanism by which allulose attenuates kidney injury.

TOPIC 08. Autonomic control of metabolism and energy homeostasis

O.48 Improved Gut Function And Prevention Of Enteric Neuropathy As Candidate Mechanisms Of Diet Induced Weight Prevention With Conditional Knockout Of Neural SARM1

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Sterile alpha and TIR motif containing 1 (Sarm1) is an inducible NADase, highly expressed in the nervous system, that is activated with injury, inflammation, and oxidative stress to promote axon degeneration and dysfunction. Previously, global knockout of Sarm1 showed evidence of partially prevented weight gain as well as metabolic improvements in high-fat diet (HFD) induced type 2 diabetes (T2D) in males. We hypothesized that this was due to the actions of Sarm1 in the nervous system. To test this hypothesis, we used Baf53b-Cre to knock out Sarm1 in all neurons (Sarm1-nKO). Both control and Sarm1-nKO mice were fed HFD for 24 weeks, starting at 5-7 weeks of age. Over the 24-week study period, Sarm1-nKO partially prevented weight gain and fat expansion in male HFD-fed mice with an even greater prevention of weight gain in female mice. Both male and female Sarm1-nKO mice on HFD had evidence of metabolic rescue with less liver steatosis and improved insulin sensitivity. Additionally, Sarm1-nKO HFD mice showed decreased food intake compared to controls. Metabolic caging showed that the prevented weight gain in Sarm1-nKO mice was not due to increased energy expenditure, locomotor activity, or thermogenesis. We are currently investigating whether Sarm1 neural knockout may prevent excess weight gain via protection against enteric neuropathy thus stabilizing gut function and hunger cues. Preliminary qPCR data show that Sarm1-nKO female mice on HFD have more regulated hunger cues than controls. Additionally, preliminary lipid absorption measurements show that female Sarm1-nKO mice have lower circulating triglycerides than controls. Through wholemount imaging of the duodenum and proximal colon, we are quantifying axon density and cell bodies throughout the myenteric and submucosa plexuses. These analyses along with functional studies including gut transit time, lipid absorption, and satiety signaling will allow us to determine whether protection of the gut and gut brain axis is driving the prevention of obesity and metabolic dysfunction in the Sarm1-nKO mice. Sarm1 inhibitors are currently under clinical development for the treatment of neurodegenerative disease. These results show that inhibition of Sarm1-dependent neurometabolic regulatory pathways also has the potential to support metabolic health in settings of obesity and T2D.

TOPIC 11. Emerging concepts and novel perspectives in autonomic neuroscience

O.49 Cerium Mimics The Torpor-like Effects Of Lithium, Altering Behavior And Physiology Via The Gut-brain Axis

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Introduction: John Cade's discovery of lithium transformed psychiatric medicine (1). We have since shown that Cade's lithium-induced guinea-pig "lethargy" involves a profound torpor-like hypothermic effect, and that lithium acts via the gut-brain axis, releasing 5-HT from enterochromaffin (EC) cells to activate vagal afferents and the area postrema (2). Cade also noted that the lanthanide element cerium reduces behavioral and physiological parameters in rats (3). We therefore tested whether cerium has lithium-like behavioral and physiological properties and whether cerium also activates a gut-brain pathway in mice.

Methods: Body temperature and locomotion were recorded by telemetry (DSI ETA-F10) in C57BL/6 mice (n=6 per group) before and after i.p. cerium chloride ($CeCl_3$) or saline control. Behavioral responses were assessed by a resident-intruder model and by conditioned taste aversion assays. Nodose ganglion and brain neuronal activation were mapped by cFos immunohistochemistry.

Results: $CeCl_3$ caused an acute dose-dependent hypothermia, lasting about 2 hours (R^2 = 0.739, $p < 0.0001$). After 0.5 mmol/kg $CeCl_3$, body temperature decreased by 7.09 ± 0.67 °C. $CeCl_3$ (0.025 mmol/kg) blunted the hyperthermic response to an intruder (saline: +0.86 ± 0.07 °C; cerium: −1.04 ± 0.47 °C, $p = 0.0024$) and $CeCl_3$ (0.1 mmol/kg) produced a conditioned taste aversion to sucrose (intake as % body weight − saline: 7 ± 0.4%; cerium: 4 ± 0.3%; $p = 0.0001$). $CeCl_3$ (0.1 mmol/kg), compared to saline, increased expression of cFos in the nodose ganglion, area postrema (AP), nucleus tractus solitarius, parabrachial nucleus and other brain nuclei also activated by lithium.

Conclusion: Cerium, like lithium, activates gut-brain circuitry to induce conditioned taste aversion and hypothermia. Dose-response studies suggest that cerium is approximately 10 times as potent as lithium. We are presently determining whether selective lesioning of 5-HT EC cells abolishes the effect of cerium, as it does for lithium. Both lithium and cerium may be activating gut-brain circuitry that induces a torpor-like state, protecting the individual from the effects of ingested toxins.

23RD Symposium - AUTONOMIC REGULATION IN CARDIOVASCULAR DISORDERS: MECHANISMS AND INTERVENTIONS

TOPIC 06. Autonomic dysfunction in neurodegenerative and orthostatic disorders

S.85 Interactions Between Stroke Volume And Cerebral Blood Flow Dynamics

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Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by an increase in heart rate of ≥30 bpm upon standing in the absence of orthostatic hypotension. Some of the most disabling symptoms reported by patients, including lightheadedness, cognitive dysfunction, and brain fog, have been associated with reductions in cerebral blood flow. Although stroke volume and carbon dioxide are known modulators of cerebral blood flow, their relative contributions to cerebral hypoperfusion in POTS remain unclear.

In this presentation, we will explore cerebral blood flow responses during orthostatic stress using two complementary experimental approaches: modulation of venous return with lower-body compression and modulation of end-tidal carbon dioxide. We will also assess blood pressure fluctuations and their influence on cerebral blood flow velocity, focusing on pressure–flow coupling during orthostatic stress.

S.86 Autonomic Dysfunction In Atrial Fibrillation- Does Targeting The Ans Alter Outcomes

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Abstract This presentation will discuss the impact of a highly prevalent cardiovascular condition, Atrial fibrillation (AF) on the autonomic nervous system (ANS). Specifically, we will define novel findings relating to abnormal volume-regulating reflexes in patients with AF and the implications of this autonomic dysfunction on the progression of AF as well as morbidity associated with AF. The role of the ANS in the pathophysiology of AF will be discussed as well as how the ANS could be harnessed to influence outcomes. Finally, a common catheter-based procedure targets the areas of the heart where volume-regulating receptors are found (pulmonary vein-atrial junction). The effect of this procedure on the ANS will be discussed.

TOPIC 01: Cardiovascular autonomic regulation in health and disease

S.87 Stellate Ganglionectomy For Ventricular Arrhythmias

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Sudden cardiac death, a leading cause of death worldwide, causes an estimated four to five million deaths per year. Among causes of sudden cardiac death due to ventricular arrhythmias, coronary artery disease is the most common. The autonomic nervous system influences pathophysiological responses to cardiovascular disease including myocardial infarction complicated by ventricular arrhythmias. Neuromodulation therapies are emerging treatments to restore sympathovagal balance through decreasing sympathoexcitation and/or increasing parasympathetic drive. Of these therapies, stellate ganglionectomy is an effective intervention for ventricular arrhythmias. Further understanding of the molecular and cellular architecture of the cardiac neuraxis and neural remodeling in disease has the potential to identify novel targets for the treatment of ventricular arrhythmias.

S.88 Carbon Dioxide As A Treatment For Orthostatic Hypotension

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Neurogenic orthostatic hypotension (nOH) is characterized by impaired autonomic cardiovascular control, resulting in profound reductions in standing blood pressure that increase risk for falls, hospitalization, cardiovascular morbidity, and cognitive decline. Despite this burden, treatment options remain limited, highlighting the need for novel, physiology-based therapeutic approaches. We present data evaluating carbon dioxide (CO2) as an acute pressor therapy in patients with nOH. In a randomized breathing trial, targeted increases in end-tidal CO2 produced dose-dependent improvements in standing blood pressure, supporting a powerful role for CO2 in hemodynamic control. To explore whether a simpler rebreathe-based approach could achieve similar pressor effects, we next tested simulated rebreathing using a combination of high CO2 and low O2. Simulated rebreathing increased standing systolic blood pressure, stroke volume, and cardiac output, and reduced hypotensive time compared to room air. However, responses did not differ significantly from those with high CO2 alone, while tolerability was substantially lower due to dyspnea. Together, these findings suggest that augmenting CO2 improves orthostatic blood pressure regulation in patients with nOH, but that CO2 delivery systems preserving oxygenation may offer a more feasible therapeutic strategy than rebreathing approaches. We are now in the early stages of testing a partial rebreathing device designed to increase inspired CO2 without causing hypoxia, as well as a direct CO2 delivery device, with findings forthcoming.

TOPIC 10. Development, aging and sex differences in autonomic function

O.50 Autonomic Adaptation In Pregnancy: Preserved Responsiveness With Reduced Modulation Across Gestation

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Introduction: Pregnancy induces profound cardiovascular adaptations, including changes in vascular resistance, cardiac output, and heart rate, which are partly regulated by the autonomic nervous system. Although a shift toward reduced parasympathetic activity has been reported, the longitudinal evolution of autonomic function and its responsiveness to physiological stressors across gestation remain incompletely defined. This study aimed to characterize trimester-specific changes in autonomic regulation and reactivity.

Methods: In this prospective longitudinal cohort, 66 healthy pregnant women were evaluated during the first (T1), second (T2), and third (T3) trimesters. Continuous cardiovascular monitoring was performed during a standardized protocol including rest, paced breathing, and a cognitive task. Heart rate variability, blood pressure, and phase synchronization indices were analysed using two-way repeated-measures ANOVA (Time × Phase).

Results: Heart rate increased across gestation, while blood pressure showed a mid-pregnancy nadir. Indices of vagal modulation declined from T1 to T3, whereas overall variability remained unchanged. No effect of gestational age was observed for sympathovagal balance, but significant Time × Phase interactions indicated attenuation of autonomic reactivity. Both vagal responses to paced breathing and sympathetic responses to cognitive stress were reduced in late pregnancy. Similarly, indices of cardio-respiratory and cardiovascular coupling showed phase-dependent changes, with reduced synchronization during paced breathing in T3.

Discussion: Our findings suggest that autonomic regulation during pregnancy is characterized by preserved responsiveness but reduced modulation. The decline in vagal activity, together with attenuated reactivity and reduced cardio-respiratory coupling, suggests reduced autonomic flexibility. These findings outline autonomic trajectories in pregnancy and may help detect early deviations linked to pregnancy-associated cardiovascular complications.

TOPIC 01: Cardiovascular autonomic regulation in health and disease

O.51 Blunted Sympathetic Vascular Transduction In Treated Compared To Untreated Hypertensive Adults

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RATIONALE: Elevated sympathetic vasomotor tone (i.e. muscle sympathetic nerve activity [MSNA]) is a common characteristic of essential hypertension (HTN). Blood pressure (BP)-lowering medications can be effective without decreasing MSNA, but the effect of chronic anti-hypertensive treatment on beat-by-beat transduction of MSNA to vasoconstriction in adults with HTN remains unknown. This study aimed to investigate sympathetic vascular transduction in untreated (UT-HTN) and treated (T-HTN) adults with HTN.

METHODS: Resting sympathetic transduction was quantified in 17 normotensive (CON; 53% females; age: 41±9 y; BMI: 32±7 kg/m2; 24-h BP: 122/72±8/7 mmHg), 12 UT-HTN (42% females; age: 40±11 y; BMI: 31±7 kg/m2; 24-h BP: 140/86±11/8 mmHg), and 21 T-HTN (off-medication [wash-out: 5 half-lives]; 62% females; age: 44±8 y; BMI: 34±7 kg/m2; 24-h BP: 144/86±17/10 mmHg) adults. Continuous measurements of MSNA (peroneal nerve, microneurography), mean arterial pressure (MAP, finger photoplethysmography), and superficial femoral artery blood flow (LBF, doppler ultrasound) were obtained during 20 minutes of supine rest. Beat-by-beat leg vascular conductance (LVC) was calculated as LBF/MAP. Sympathetic transduction to LVC and MAP were quantified using signal averaging. Data were analyzed via mixed-effects model (Group×Cardiac Cycle) with sex and BMI as covariates.

RESULTS: Resting MSNA burst frequency (CON: 18±11 vs. UT-HTN: 22±9 vs. T-HTN: 22±11 bursts/min, P=0.651) and LVC (CON: 1.13±0.42 vs. UT-HTN: 0.87±0.46 vs. T-HTN: 1.01±0.47 mL/min/100mmHg, P=0.250) were not different between groups, while BP during supine testing was higher in UT-HTN and T-HTN than in CON (CON: 117/71±12/11 vs. UT-HTN: 135/86±14/12 vs. T-HTN: 140/90±10/10 mmHg, P<0.001). Compared to CON and UT-HTN, T-HTN exhibited blunted sympathetic vascular transduction to all (CON: -8.5±5.9% vs. UT-HTN: -8.0±3.1% vs. T-HTN: -3.8±2.4%, interaction: P<0.001) and multiple (CON: -11.5±7.5% vs. UT-HTN: -10.6±5.1% vs. T-HTN: -5.4±4.4%, interaction: P<0.001) MSNA bursts. An interaction effect was observed for sympathetic transduction to BP following all (CON: 3.1±1.5 vs. UT-HTN: 3.3±1.1 vs. T-HTN: 2.7±1.3 mmHg, interaction: P=0.039), but not multiple (CON: 4.1±1.9 vs. UT-HTN: 3.9±1.3 vs. T-HTN: 3.7±2.0 mmHg, interaction: P=0.287), MSNA bursts.

CONCLUSION: Compared to CON, sympathetic vascular transduction was attenuated in T-HTN but was preserved in UT-HTN. These findings suggest vascular desensitization with chronic anti-hypertensive treatment that persists following washout of BP-lowering medications.

24TH Symposium - CIRCADIAN SYSTEM AND AUTONOMIC REGULATION

TOPIC 03. Sleep, circadian rhythms and the autonomic nervous system

S.89 Anatomy Of The Circadian System

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The circadian system includes the suprachiasmatic nucleus (SCN), which is the circadian pacemaker that coordinates intrinsic cellular circadian oscillators in the rest of the nervous system and peripheral organs. This coordination is mediated by humoral signals, such as melatonin and cortisol, and by sympathetic and parasympathetic outputs. Most SCN neurons are GABAergic and encompass several subpopulations expressing distinct repertoire of neuropeptides, including vasoactive intestinal polypeptide (VIP), arginine vasopressin (AVP) and others. SCN neurons fire primarily during daytime, primarily via entrainment by light mediated by input melanopsin ganglion cells (retinohypothalamic tract). The SCN also receives light inputs from the intermediate lateral geniculate nucleus, as well as inputs from the paraventricular nucleus of the thalamus, median raphe, and several hypothalamic nuclei. The SCN provide outputs to their targets both directly and via neurons in the subparaventricular zone (SPVZ) in the hypothalamus. These outputs reach the median preoptic nucleus, medial preoptic area (MPO the thermoregulatory setpoint initiating heat dissipation), ventrolateral preoptic area (VLPO, involved in sleep initiation) and, most importantly, the paraventricular nucleus (PVH) and dorsomedial nucleus (DMH). The PVH contains neurons that promote release of melatonin during darkness mediated by superior cervical ganglion output to the pineal gland, and are the target of GABAergic SCN inhibition during daytime. Corticotropin releasing hormone neurons in the PVH mediate circadian variations of cortisol secretion. Distinct subpopulations of sympathetic or parasympathetic neurons of the PVH receive inputs from different SCN neurons either directly or via the SPVZ, and mediate circadian fluctuations of blood pressure, heart rate, blood glucose, and other responses via their input to the medulla or spinal cord. The DMH is critical mediator of circadian influences on levels of arousal, sympathetic activity, and feeding behavior. Via an inhibitory relay on the SPVZ, the SCN triggers disinhibition of glutamatergic and GABAergic neurons of the DMH. Glutamatergic DMH outputs activate arousal-promoting neurons, including orexin/hypocretin neurons in the posterior lateral hypothalamus and noradrenergic neurons in the locus coeruleus, which also promote sympathoexcitation, whereas GABAergic output from the DMH inhibits sleep-promoting neurons of the VLPO. Circadian circuit disturbances in neurodegenerative and other disorders impair cardiovascular health and cognition.

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TOPIC 03. Sleep, circadian rhythms and the autonomic nervous system

S.89 Circadian Disorders And Autonomic Nervous System

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The autonomic nervous system (ANS) plays a pivotal role in the regulation of the sleep-wake cycle and is a critical determinant of physiological homeostasis. Circadian sleep-wake disorders result from persistent misalignment between the endogenous circadian clock and the external light-dark cycle, disrupting both the timing and quality of sleep. Conditions including delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, and shift work disorder are characterized by chronic circadian disruption, frequently leading to insufficient or fragmented sleep. This circadian misalignment profoundly alter autonomic regulation. Acutely, this imbalance induces a state of physiological hyperarousal, characterized by increased heart rate, reduced heart rate variability, elevated blood pressure, and enhanced cortisol secretion. Over time, sustained sympathetic predominance may drive the development of cardiovascular and metabolic complications, including hypertension, endothelial dysfunction, systemic inflammation, insulin resistance, and an increased risk of cardiovascular disease.

The relationship between circadian sleep disorders and autonomic dysfunction is therefore bidirectional and clinically relevant. Sleep and circadian disturbances impair autonomic regulation, whereas autonomic imbalance further compromises sleep quality and circadian stability. Recognizing this interplay has important diagnostic and therapeutic implications. Patients presenting with autonomic symptoms should be systematically evaluated for underlying circadian and sleep disorders, while individuals with chronic sleep disturbances should be assessed for autonomic dysfunction. Early identification and integrated management may restore autonomic balance, improve sleep outcomes, and ultimately reduce the long-term burden of cardiovascular and metabolic disease.

TOPIC 03. Sleep, circadian rhythms and the autonomic nervous system

S.90 Resetting The Circadian Clock: Emerging Approaches

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TOPIC 03. Sleep, circadian rhythms and the autonomic nervous system

O.50 Nocturia And Sleep In Parkinson's Disease

Stefania Diaconu (1) - Laura Irincu (1) - Larisa Ungureanu (1) - Iulia Murasan (1) - Diana Batrinu (1) - Cristian Falup-pecurariu (1)

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Background: Nocturia has a high prevalence in Parkinson's Disease (PD) and is known to be a bothersome symptom for people with Parkinson's disease (PwPD). Objective: to characterize nocturia in a sample of PwPD, in relation to sleep, fatigue and other non-motor symptoms (NMS).

Methods: we assessed 130 PwPD using a comprehensive battery of scales, which includes the Non-Motor Symptoms Questionnaire (NMSQ), International Parkinson and Movement Disorder Society Non-Motor Rating Scale (MDS-NMS), Parkinson's Disease Sleep Scale version 2 (PDSS-2), Parkinson's Disease Questionnaire (PDQ-39), The Overactive Bladder Questionnaire-Short form (OABq-SF), and the Parkinson's Fatigue Scale (PFS-16). Results: according to the positive answers to the item of the NMSQ related to nocturia, patients were divided into PwPD + nocturia, and PwPD nocturia. Nocturia was reported by 112 patients (86.15%). Quality of life in PwPD + nocturia was worse than in PwPD nocturia, according to the PDQ-39 scores (13.32 9.00 vs. 26.29 14.55, $p < 0.001$). Sleep was significantly disturbed in PwPD + nocturia compared to PwPD nocturia, according to the total scores of various scales, such as PDSS-2, PFS-16. PwPD who complained of nocturia presented higher scores of several NMS. Conclusions: nocturia has a high prevalence in PwPD and it is associated with impaired sleep, fatigue, and reduced quality of life.

TOPIC 03. Sleep, circadian rhythms and the autonomic nervous system

O.51 State-dependent Modulation Of Upper Airway Patency In Obstructive Sleep Apnea: Differential Control Of Hypoglossal And Glossopharyngeal Motor Systems

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Introduction: Upper airway patency is maintained by coordinated activity of dilator muscles, including the genioglossus (GGm) and stylopharyngeus (SPm), controlled by the hypoglossal (HMS) and glossopharyngeal (GMS) motor systems. These muscles serve dual roles, contributing to inspiratory airway dilation while facilitating control of the pharyngeal-esophageal transition during swallowing. This functional dichotomy requires precise coordination, and its disruption is central to obstructive sleep apnea (OSA). While HMS control has been extensively studied, the premotor organization and physiological role of the GMS remain largely unknown despite its importance for lateral pharyngeal wall stability in particular during sleep.

Methods: We combined electrophysiology and viral circuit tracing to define premotor pathways controlling HMS and GMS. Motor nerve activity was recorded using an in situ perfused brainstem preparation, which preserves respiratory-deglutitive crainail nerve brainstem networks. Viral tracing with recombinant pseudorabies viruses (PRV 512 and PRV 614) injected into GGm and SPm enabled simultaneous mapping of premotor circuits and identification of convergent and divergent neuronal populations.

Results: Hypoglossal and glossopharyngeal nerves showed similar pre-inspiratory and inspiratory discharge patterns, indicating a shared respiratory drive. Activation of the REM-on center in the pons selectively suppressed HMS but spared GMS activity, suggesting that the GMS acts as a safeguard during REM sleep. First-order motor neurons were localized to the ventral hypoglossal nucleus and compact formation of the nucleus ambiguus. Second-order pre-motor neurons showed convergence within the pre-Bötzinger complex, whereas premotor neurons in the nucleus of the solitary tract were largely distinct. HMS premotor neurons were identified in the Kölliker-Fuse nucleus, while GMS premotor neurons localized to the adjacent Sub-trigeminal nucleus know for swallowing control. GMS output showed marked reduction in drive after acute intermittent hypoxia in situ, suggesting that progressive GMS impairment may worsen OSA by introducing lateral pharyngeal wall collapse.

Conclusion: These findings identify a previously unknown GMS premotor system and demonstrate state-dependent modulation of upper airway control. Hypoxia vulnerability of preserved GMS activity during REM provides new mechanistic insight into OSA.

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TOPIC 01. Cardiovascular Autonomic Regulation In Health And Disease

P.1 - Attenuating Cardiac Sympathetic Tone Via Cryoneurolytic Stellate Ganglion Ablation

Rami Aladham (1)* - *Wei-hsin Chung (1)* - *Sahil Haridas (1)* - *Lily Defelice (1)* - *Steven Cha (1)* - *Shyue-an Chan (2)* - *Jeffery Ardell (1)* - *Olujimi Ajijola (1)* - *Peter Hanna (1)

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Introduction: Stellate ganglion blockade (SGB) provides temporary control of refractory ventricular arrhythmias by reducing sympathetic flow to the heart. However, current percutaneous approaches are limited by short duration of effect, creating a need for longer-lasting sympathetic modulation without more invasive permanent sympathectomy. The objective of this study was to determine the efficacy and duration of stellate ganglion cryoneurolytic ablation in attenuating evoked cardiac sympathetic responses.

Methods: We conducted acute cryoablation studies in 6 Yorkshire pigs and chronic studies in 10 Yucatan minipigs (7 cryoablation, 3 sham controls). In acute studies, we measured hemodynamic and cardiac neurotransmitter release by fast-scanning cyclic voltammetry at baseline, post-cryoablation, after 3-hour recovery, and after complete sympathetic chain surgical transection. For chronic studies, we performed right stellate ganglion (RSG) cryoneurolytic ablation and reassessed autonomic responses one month later during terminal procedures.

Results: Cryoneurolytic stellate ganglion ablation attenuated evoked responses in both acute and chronic phases. Sympathetic attenuation was anatomically restricted to the ablation site. Targeting the T1 stellate ganglion alone was sufficient to eliminate the majority of evoked sympathetic cardiac effects.

Conclusion: Cryoneurolytic stellate ganglion ablation effectively provides sustained cardiac sympathetic modulation, offering a promising intermediate-duration treatment for refractory ventricular arrhythmias.

P.2 - Comparison Of Ai-based And Manual Computational Approaches For Baroreflex Analysis Using The Modified Oxford Method In Normotensive Lewis Rats

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Introduction: The Modified Oxford method is commonly used to assess baroreflex function but requires nonlinear regression analyses that can be time-consuming when applied to large datasets. Recent advances in large language models (LLMs) may facilitate automated physiological data analysis; however, their reliability for quantitative modeling remains unclear. This study evaluated the accuracy, repeatability, reproducibility, and computational efficiency of GPT-5.5 Instant model compared with conventional manual nonlinear regression for baroreflex analysis.

Methods: In anesthetized adult male Lewis rats (n=8), mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA) were measured during sequential intravenous administration of sodium nitroprusside and phenylephrine. Baroreflex curves were modeled using a four-parameter logistic function, and range (%), gain (%/mmHg), MAP50 (mmHg), and R^2 were derived. Analyses were performed using OpenAI's ChatGPT via both the Free and Plus tiers, utilizing the GPT-5.5 Instant model (accessed June 2026) and compared with manual nonlinear regression. Two users conducted three repeated analyses per platform using an identical prompt with memory disabled. Accuracy, repeatability, reproducibility, Bland-Altman agreement, and analysis time were assessed.

Results: Both Free ChatGPT and ChatGPT Plus, utilizing the GPT-5.5 Instant model, generated baroreflex parameters that closely matched manually derived values. Across platforms and users, percentage error relative to manual calculations remained below 0.4% for all parameters. Mean absolute errors for Range, Gain, and MAP50 were 0.036, 0.011, and 0.031, respectively. Repeatability and reproducibility were excellent, with standard deviations ≤0.0002 and coefficients of variation approaching zero across repeated analyses. Bland-Altman analysis demonstrated minimal bias relative to manual calculations (Range: 0.007–0.008; Gain: 0.003; MAP50: 0.000) with narrow limits of agreement. Model fit was identical across analytical approaches (R^2=1.00). Both AI platforms substantially reduced analysis time compared with manual regression, with ChatGPT Plus exhibiting the shortest processing times.

Conclusion: Under standardized prompting conditions, GPT-5.5 Instant accurately reproduced manual nonlinear regression outcomes for baroreflex analysis while substantially reducing analysis time. Although minor deviations from manual calculations persisted, agreement, repeatability, and reproducibility were excellent across users and trials. These findings support the use of GPT-5.5 as efficient analytical aid for nonlinear physiological modeling while highlighting the importance of independent verification for quantitative applications.

P.3 - Maintenance Of Brainstem Cholinergic Integrity After Isoflurane Anesthesia And Surgical Stress: Translational Relevance For Autonomic Research

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INTRODUCTION: The brainstem is the primary regulatory centre for cardiovascular and respiratory control, where cholinergic signaling plays a vital role in homeostatic balance. Preclinical outcomes in autonomic neuroscience can be significantly confounded by the choice of anaesthetic, as certain agents alter central enzymatic activity. In previous studies we demonstrated that the ketamine/xylazine mixture reduced cholinesterase activity in the brainstem of male rats, potentially masking or skewing physiological results. Therefore, evaluating whether isoflurane, a widely used volatile anaesthetic, interferes with this region is essential for both experimental validity and clinical perioperative safety. METHODS: Brainstem cholinesterase (ChE) activity was investigated in 10-12 week-old male and female Wistar rats under three protocols (Ethical Approval 04/2024): Surgery+Anesthesia (P1), combining femoral catheterization under isoflurane (ISO, 4% induction, 2.5% maintenance) and 48h recovery; Isoflurane-only (P2), with isolated pharmacological exposure to ISO and 48h recovery. Naïve (P3), consisting of age-matched control animals that underwent no procedures and were sampled concurrently with the experimental protocols. ChE activity was determined by colorimetric assay and analyzed by one-way ANOVA ($p<0.05$). RESULTS: In both male and female rats, brainstem ChE activity remained stable across all groups. No significant differences were observed in P1 or P2 compared to the Naïve control (P3) 48 hours after the procedures. Unlike other anaesthetic regimes, neither the pharmacological effect of ISO nor the added surgical trauma induced persistent alterations in the cholinergic status of this primary autonomic centre in either sex. CONCLUSION: These findings demonstrate that ISO maintains enzymatic homeostasis in the brainstem, suggesting it is a biochemically neutral agent for central autonomic studies. This stability is crucial for research evaluating cardiorespiratory control and cholinergic signaling in this region, as it ensures a reliable experimental baseline. From a translational perspective, the lack of central cholinergic interference by ISO may contribute to reduced autonomic imbalance during the post-anesthetic period, highlighting its potential for optimizing clinical outcomes. FUNDING: FAPES Grant code: 21/2023 - 749/2024. MSM; LJC; VSM; KBS; BFS; JGMA; TJB: CAPES (Grant Code 01). GGN; BML; PBSA: FAPES. AB: UFES (PIBIC UFES). KNS: CNPq/FAPES 2025-H5S1W fellowship; CNPq/MCTI/FNDCT Nº 44/2024 (402130/2025-1).

P.4 - Efficacy Of Six Weeks Of Supervised Yoga On Pain Perception And Autonomic Profile In Fibromyalgia Patients: A Randomised Controlled Trial.

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Title: Efficacy of six weeks of supervised Yoga on pain perception and autonomic profile in Fibromyalgia Patients: A Randomized Controlled Trial.

Study Design: Randomized controlled trial

Methods and Material: Eighty female FM patients were recruited and randomized into Yoga and standard care group. Assessment for pain perception was done using VAS, FIQ and Offset analgesia (OA) paradigms at C8 dermatome of the left forearm at Day 0 and 43. A standard battery of non-invasive tests of autonomic function and heart rate variability (5 min duration) was used for autonomic assessment. This was followed by scoring autonomic symptom severity at baseline. Biochemical analysis was done to evaluate pain facilitation and inhibition.

Statistical analysis: Normality test was done using D'Agostino and Pearson normality test and group data analysis was done using STATA 14 software. Parametric or non-parametric tests were applied based on data normality, using a significance level of $p < 0.05$.

Results: Findings provide evidence of association between FM patients participating in yoga classes and reduced fibromyalgia - related symptoms as assessed by VAS and FIQ scores after 6 weeks. Significant difference between VAS ($p=<0.0001$) and FIQ ($p=<0.0001$) scores post 6 weeks was observed between groups. Significant increase in change in VAS minimum (ΔOA), Latency, OA index was observed after yoga in all the offset analgesia paradigms. Autonomic Function testing revealed significantly reduced mean heart rate and increase in change in Diastolic Blood Pressure (Δ DBP) after yoga. Significant increase in pain inhibition and decrease in pain facilitation biochemicals was observed at the end of yoga.

Conclusions: Yoga as a holistic approach helps in ameliorating pain and other fibromyalgia related symptoms after 6 weeks. Additional randomized controlled trials with larger sample sizes are needed to more fully understand this relationship.

Key-words: Visual analogue scale (VAS), Quantitative sensory testing (QST), Offset Analgesia (OA), Heart Rate Variability (HRV), Fibromyalgia Impact Questionnaire (FIQ)

P.5 - Effects Of Lumacaftor On Blood Pressure And Cerebral Blood Flow In A Conscious Rat Model Of Hypertension And Prediabetes

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Approximately 75% of patients with type 2 diabetes also have hypertension, and over half of hypertensive patients exhibit impaired glucose regulation. Both conditions are characterised by chronic sympathetic overactivation, suggesting a shared autonomic mechanism contributing to dysregulation of blood pressure (BP) and blood glucose. This overlap highlights an important opportunity for therapeutic intervention targeting shared pathophysiological pathways, with the potential to improve cardiovascular and metabolic outcomes. We have previously demonstrated that cerebral blood flow (CBF) and the brain's glymphatic waste clearance system are disrupted in hypertensive and prediabetic rats, supporting a mechanistic link between autonomic dysregulation and impaired neurovascular function. Lumacaftor, a CFTR modulator approved for cystic fibrosis, has been reported to improve cerebrovascular reactivity in preclinical models of heart failure and stroke. We therefore tested the hypothesis that lumacaftor would improve CBF and glymphatic function in our model of combined hypertension and prediabetes.

Male spontaneously hypertensive rats were fed a high-calorie (high-fat, high-fructose) diet for 15 weeks. Animals underwent glucose tolerance testing and were instrumented for long-term, conscious measurements of arterial BP and CBF. Following a baseline period, rats received 17 days of treatment with lumacaftor (2 mg/kg/day, i.p.; n=5) or vehicle (n=4). At the end of the protocol, glymphatic function was assessed by tracer infusion into the cisterna magna under ketamine/medetomidine anaesthesia.

Lumacaftor treatment did not alter caloric intake (73±12 vs. 66±6 kcal/day), glymphatic function (52±9 vs. 55±33 AU), conscious CBF (3.8±0.8 vs. 4.3±1.1 mL/min), cerebrovascular resistance (41±15 vs. 39±5 mmHg·mL/min), heart rate (283±12 vs. 280±15 bpm), pulse pressure (60±4 vs. 60±3 mmHg), or glucose intolerance (1052±59 vs. 1114±26 AUC). However, chronic blood pressure measurements revealed a significant reduction in lumacaftor-treated rats (−7±10 vs. +14±9 ΔmmHg, P=0.0051), indicating a sustained antihypertensive effect independent of metabolic and cerebrovascular changes.

Despite no measurable improvements in CBF or glymphatic function, lumacaftor significantly reduced blood pressure in a hypertensive/prediabetic model. The mechanisms underlying this hypotensive effect warrant further investigation to evaluate potential long-term cerebrovascular and metabolic benefits.

P.6 - Renal Nerve Afferents Drive Preferential Renal Sympathoexcitation In Response To Acute Renal Ischemia/reperfusion In Rats.

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Introduction: Renal ischemia/reperfusion (IR) increases renal sympathetic nerve activity (rSNA) and impairs renal function. However, the role of renal afferent transient receptor potential vanilloid type 1 (TRPV1) fibers in acute renal IR remains unclear. We therefore tested the hypothesis that renal IR increases rSNA through activation of renal afferent nerves.
Methods: Two series of experiments were performed in adult male Wistar rats (Ethical Committee -7621161222). IR was induced by total obstruction of blood flow to the left kidney by clamping the renal artery for 60 minutes. In the first series of experiments, reperfusion was monitored for 120 minutes. We recorded mean arterial pressure (MAP), heart rate (HR), rSNA, and splanchnic sympathetic nerve activity (sSNA) in 8 normal IR and 6 left kidney deafferented IR rats (IR+ARD). Renal deafferentation was achieved by applying capsaicin (33 mM) to the left renal nerve two weeks prior to the experiments. Blood samples were collected before ischemia and at the end of reperfusion for total and differential leukocyte counts. Renal function was assessed in the second experimental series using metabolic cages. Urine samples were collected at 24 and 48 hours after reperfusion.
Results: Renal ischemia significantly increased rSNA by 23% (20 min: 0.07 ± 0.04 mV·s), but had no effect on sSNA. The increase in rSNA appears to be mediated by activation of renal afferent fibers, as IR significantly reduced rSNA in the IR+ARD group, reaching a maximal decrease of 22% in firing frequency (180 min: 62 ± 29 Δspikes/s) and 41% in amplitude (0.29 ± 0.12 mV·s), accompanied by hypotension and bradycardia. No significant differences were observed between groups in the blood leukocyte profile. In contrast, renal IL-6 levels were significantly reduced in the IR+ARD group, suggesting attenuated renal inflammation in renal deafferented IR rats. Regarding renal function, animals subjected to prior deafferentation exhibited reduced tubular injury from 24 hours onward, as indicated by lower levels of γ-GT, β2-microglobulin, and neutrophil gelatinase-associated lipocalin (NGAL).
Conclusion: The results indicate that renal TRPV1 afferent fibers drive a preferential increase in rSNA and contribute to intrarenal inflammation and tubular injury following renal ischemia–reperfusion.
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P.7 - Pyridostigmine For Autonomic Dysfunction And Symptoms In Post-COVID- 19 Condition: A Randomized Double-blind Placebo-controlled Crossover Clinical Trial.

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Introduction. Fatigue is among the most prevalent and disabling manifestations in Post COVID-19 Condition (long COVID), compromises 10- 30% of infected subjects (estimated 200 million people worldwide), and impairs functional capacity and quality of life. Autonomic dysfunction has been proposed as a potential mechanism underlying these symptoms and therefore, is promising target for pharmacological treatment. Pyridostigmine bromide is a reversible acetylcholinesterase inhibitor, thus causing an indirect parasympathetic activation and has been shown to reduce markers of autonomic dysfunction in both experimental models and in the clinical setting. Pyrirdostigmine has been commercially available for decades mainly for

alleviate skeletal muscle weakness in patients with myasthenia gravis. Therefore, the purpose of this study as to determine whetherpyridostigmine bromide could provide a therapeutic strategy to alleviate fatigue, improve dysautonomia symptoms and enhance quality of life in individuals with post-COVID-19 Condition.
Methods. A randomized, double-blind, placebo-controlled, crossover clinical trial was conducted. Participants received pyridostigmine bromide (60 mg, three times daily) or placebo for 30 days, respecting a 2-day washout period between
treatments. Assessments included the Chalder Fatigue Scale, WHOQOL-Bref, and COMPASS-31 questionnaires; echocardiography; 12-lead electrocardiogram; cardiovascular autonomic tests (Valsalva maneuver, deep breathing, active standing); handgrip strength; maximal inspiratory pressure; spirometry; and cardiopulmonary exercise testing.
Results. Fifteen participants (8 male, 7 female; age 42±9 years) were enroled. The pyridostigmine bromide administration significantly improved fatigue (Chalder Fatigue Scale, p<0.01), dysautonomia symptoms (COMPASS-31, p<0.001), and quality of life (WHOQOL-Bref domains “perception of quality of life,” p=0.003; “satisfaction with health,” p=0.001) compared with placebo and baseline. Maximal inspiratory pressure (p=0.01) and peak expiratory flow (p=0.02) also improved with pyridostigmine and placebo, while no changes were observed in autonomic test responses or aerobic capacity.
Conclusion. Pyridostigmine bromide effectively reduced fatigue and dysautonomia symptoms and enhanced quality of life in patients with Post COVID-19 Condition. These findings support its potential as a therapeutic strategy to promote functional recovery and reintegration into daily activities after COVID-19.

Disclosure. The authors declare that they have no conflict of interest. This study was supported by Brazilian Research Agencies (CNPq, CAPES, FINEP,FAPERJ).

P.8 - Short-term Heart Rate Variability Assessment Shows Transient Vagal Dysfunction At 4 Weeks Post-surgery For Head And Neck Cancer

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Introduction: Multimodal treatment of head and neck cancer involving neck dissection and adjuvant therapy could potentially lead to autonomic dysfunction due to the close proximity of critical neurovascular structures involved in autonomic control. Short-term heart rate variability (HRV) is an established marker of autonomic modulation of resting heart rate by the sympatho-vagal system. The present study longitudinally evaluated HRV in patients with head and neck cancer at baseline, 4 weeks after surgery (post-Sx) and 3 months after adjuvant therapy (post-AT).

Methods: Patients with histologically confirmed head and neck cancer who fulfilled the inclusion and exclusion criteria underwent HRV assessment at baseline, 4 weeks post-Sx, and 3 months post-AT. Five minutes of single-channel Lead-II ECG was acquired in the supine position using a digital data acquisition system (PowerLab, ADInstruments, New Zealand). RR intervals extracted from the processed ECG signal were subjected to time- and frequency-domain analyses using the HRV analysis module of LabChart Pro – 8 software (ADInstruments, New Zealand). Longitudinal analysis of the data was performed using appropriate statistical tests.

Results: Longitudinal data from 13 male patients aged 33 to 68 years who completed the scheduled follow-ups were included for analysis. Overall variability in HRV as signified by the total power declined at 4 weeks post-Sx [580 (369-2086) ms2 at baseline vs 292 (173-538) ms2; p = 0.006] and recovered to values not significantly different from baseline at 3 months post-AT [602 (288-706) ms2]. Absolute High Frequency (HF) power representing vagal modulation declined significantly 4 weeks post-Sx [105 (81-241) ms2 at baseline vs 57 (33-71) ms2] with a similar pattern of recovery at 3 months post-AT. However, low-frequency power did not show any significant power (RMSSD) revealed similar patterns.

Conclusion: Longitudinal analysis of the initial HRV data showed transient vagal dysfunction at 4 weeks post-surgery for head and neck cancer, which recovered at 3 months post-adjuvant therapy.
change across assessment time points. Time domain correlates of total (SDNN) and HF

P.9 - Sted Microscopy And Transmission Electron Microscopy Reveal Mitochondrial Reverse Remodelling Following Respiratory Heart Rate Variability Pacing In Heart Failure

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Background: Respiratory heart rate variability (RespHRV) is a natural beat-to-beat variation in heart rate linked to respiration that is lost in heart failure. We have previously shown that restoring RespHRV using a novel biofeedback pacemaker improves cardiac function in an ovine model of heart failure with reduced ejection fraction (HFrEF). Recent proteomic and metabolomic analyses suggested improved mitochondrial function as a potential mechanism underlying this response. We therefore investigated whether RespHRV pacing restores mitochondrial structure in the failing heart.

Methods: Heart failure was induced in sheep by sequential coronary microembolisation. Animals were assigned to control (n=5), heart failure (HF; n=5), or heart failure treated with RespHRV pacing for two weeks (HF+R; n=5). Left ventricular tissue was analysed using stimulated emission depletion (STED) microscopy of TOMM20-labelled mitochondria and transmission electron microscopy (TEM) of mitochondrial ultrastructure. Proteomic and metabolomic analyses were used to provide mechanistic context.

Results: STED microscopy demonstrated a highly organised columnar arrangement of mitochondria in control myocardium that was disrupted in HF. Directionality analysis revealed loss of mitochondrial alignment in HF that was restored following RespHRV pacing ($p=0.051$). Quantification of TOMM20 labelling demonstrated a significant increase in TOMM20-positive area in HF+R compared with HF ($p=0.005$). TEM revealed marked disruption of mitochondrial cristae architecture in HF hearts, characterised by a significant reduction in cristae density compared with controls ($p<0.001$). Following two weeks of RespHRV pacing, cristae density was significantly increased compared with HF ($p<0.001$) and mitochondrial ultrastructure restored towards the control phenotype despite no change in total mitochondrial area fraction. Complementary proteomic analyses demonstrated restoration of mitochondrial proteins associated with oxidative metabolism and fatty acid β-oxidation, while paired plasma metabolomic analyses showed reductions in circulating long-chain acylcarnitines following pacing, consistent with improved mitochondrial oxidative function.

Conclusions: RespHRV pacing induces reverse remodelling of mitochondrial architecture in the failing heart. STED microscopy and TEM demonstrate restoration of mitochondrial organisation and cristae density, providing a structural basis for improved mitochondrial function. These findings identify mitochondrial recovery as a key component of the therapeutic response to RespHRV pacing and highlight the value of advanced imaging approaches for understanding mechanisms of cardiac repair.

P.10 - Preferential Renal Tubular Injury And Increased Renal Sympathetic Activity Occur During The Early Stages Of Doca-salt Hypertension In Male Rats

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Neurogenic hypertension has a greater impact on target organs, such as the kidneys. We investigated possible alterations in urinary mediators in DOCA-Salt rats (No: 3812260824). Male Wistar rats (± 180 g) were divided into UNx (unilateral nephrectomy) and DOCA (unilateral nephrectomy plus deoxycorticosterone acetate (DOCA) (1st [20], 2nd-3rd [12], and 4th-5th [6] mg/kg, weeks, respectively). DOCA received a daily solution of sodium chloride (1%) + potassium chloride (0.2%), while rats UNx received normal water. Rats were evaluated after 3 weeks and 5 weeks of treatment. Lactate dehydrogenase (LDH) and gamma-glutamyl transferase (GGT) activity, levels of total proteins, epidermal growth factor (EGF), cystatin C, β2-microglobulin (β2M), alpha-1 acid glycoprotein (AGP), and neutrophil gelatinase-associated lipocalin 2 (NGAL) were evaluated in urine as markers of kidney function. The kidney was also histologically stained. Results are expressed as mean ± standard deviation, analyzed using two-way ANOVA and Bonferroni post-hoc test. Mean arterial pressure values of 134* ± 7.9 to 169*# ± 9.6 mmHg at 3 and 5 weeks, respectively. DOCA-Salt induced a significant increase in resting renal sympathetic nerve activity (rSNA) compared with UNx at both 3 weeks (110 ± 8.7 to 158* ± 12.5); and 5 weeks (80 ± 19.0 to 165* ± 9.6) spikes/s. The rSNA baroreflex sensitivity decreases (UNx: Δ −2.012 ± 0.12, n = 3 vs. DOCA: Δ −1.584* ± 0.11 spikes/s/mmHg, n = 6) to a similar extent after 3 weeks and 5 weeks of DOCA-Salt treatment. LDH activity, a marker of glomerular renal injury related to cell death, and GGT activity, a marker of proximal tubular injury, were significantly higher in DOCA-Salt groups compared to UNx. In the 3rd week of the experimental period, LDH levels were statistically higher, while GGT remained elevated in both the 3rd and 5th experimental weeks. EGF, β2M, Cystatin C, and total protein levels increased after 3 weeks and remained elevated relative to respective controls. The other mediators did not differ among groups. Additionally, renal histological evaluation revealed differences between DOCA-Salt and UNx. These findings indicate that preferential renal tubular injury associated with increased rSNA occur during the early stage of DOCA-Salt hypertension.

P.11 - The A Isoform Of Alpha1 Adrenergic Receptors In Cardiac Vagal Nucleus Ambiguus Increases Heart Rate Through Increased Gabaergic Inhibition

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Cardiac vagal neurons (CVN) are cardioinhibitory neurons that reside in nucleus amgbiuus (NA) and rely on strong tonic GABAergic inhibition mediated by GABAAR containing the δ-subunit (GABAAδR). GABA receptors can be regulated by neuromodulatory signaling like G-protein-coupled receptors (GPCRs). Although α1-ARs are canonically excitatory, activation of α1-ARs, a Gq-GPCR, increased GABAergic inhibition in CVN NA. Additionally, the A isoform of α1-ARs (α1A-ARs) activates protein kinases which in other brain regions increases GABAAδR activity. Therefore, the functional role of α1-ARs in CVN-mediated heart rate (HR) regulation remains unclear. We hypothesized that α1A-ARs mediates direct inhibition (not excitation) of CVN NA. To test this, urethane anesthetized wild-type (WT) mice were bilaterally nanoinjected with the α1-AR agonist, phenylephrine (PE; 60 nL; 10 nL/s), into NA while recording HR. PE produced a significant tachycardic response. In a transgenic model where α1A-AR is knocked down (α1A-ARNull; B6.129X1-Adra1atm1Pcs/J), PE failed to produce this tachycardia. Nanoinjections were repeated in our mouse model lacking GABAAδR in ChAT-positive motor neurons (ChAT- δNull). Similar to α1A-ARNull, ChAT- δNull mice failed to elicit a PE-induced tachycardia. Comparisons confirmed a significant difference between genotypes, with post-hoc analysis revealing differences between WT vs α1A-ARNull and WT vs ChAT- δNull. These findings confirm that α1A-ARs in CVNs mediate increased HRs in response to PE, likely through increasing GABAAδR activity. Optogenetic stimulation of dopamine β-hydroxylase positive terminals in NA confirmed that endogenous norepinephrine (NE) release into NA also elicited a tachycardic response. Immunohistochemistry confirmed α1A-AR expression in retrogradely labeled CVN NA. To examine the role of α1A-AR in disease, previous work demonstrated that 15 days on HFD caused NA-dependent blunting in cardiovagal output. α1A-ARNull mice were resistant to HFD-induced cardiovagal blunting compared to WT controls. These studies show a critical role of α1A-ARs in HR regulation, and its alterations in HFD. Future studies will utilize whole-cell patch-clamp from CVNs to determine whether α1A-AR effects originate from receptors on CVNs themselves or are mediated indirectly through local inhibitory neurons.

P.12 - Mesenteric Venous Blood Volume Shift By Adrenergic Blockade In Conscious Hypertensive Rats.

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Introduction: Venous reservoir beds such as the mesenteric circulation contain two-thirds of blood volume at rest and receive dense sympathetic innervation, suggesting a critical neurogenic role for the mobilization of blood between the venous and arterial circulations. Adrenergic receptors (AR) are differently distributed among mesenteric arteries and veins, with alpha2-ARs more selectively associated with venoconstriction. We have shown previously that spontaneously hypertensive rats (SHR) have reduced venous capacity to accommodate excess volume within the mesenteric vascular bed, leading us to propose that mesenteric venoconstriction contributes to sustained hypertension in SHR. We hypothesized that targeting the venous circulation with alpha2-AR blockade would enable a blood volume shift towards the mesenteric venous capacitance vessels and therefore reduce hypertension.

Methods: To quantify volume shifts within the mesenteric vascular bed, SHR (n=6) were instrumented with both arterial and venous mesenteric flow probes. Arterial and venous pressures were measured by implanted telemeters, along with an intravenous line. Conscious rats were fully recovered from the instrumentation surgery for ~2 weeks and acclimatized to recording conditions. A baseline recording was performed before intravenous alpha2-AR blockade (0.1 mg/kg).

Results: Baseline arterial blood pressure and mesenteric blood flow were 159±17 mmHg and 13.4±2.5 ml/min, respectively. The maximum reduction of blood pressure after bolus was -24±10 mmHg. Both mesenteric arterial and venous flow fell with decreasing arterial pressure, however, total mesenteric blood volume flow showed a net increase of 1.0±1.1 ml/min ($P<0.01$), leading to an acute blood volume shift of ~5% into the mesenteric bed. The arterial flow pulsation increased from 26.4±2.9 to 32.4±5.6 ml/min ($P<0.04$), while arterial pulse pressure remained constant (62±6 vs. 63±8 mmHg).

Conclusion: The reduction of blood pressure by alpha2-AR blockade was accompanied by a blood volume shift towards capacitance vessels in the mesenteric vascular bed. SHR have an impaired mesenteric venous capacity due to increased sympathetic activity, but our results show that the 'buffering capacity' of the venous reservoir can be improved, albeit acutely. Our findings suggest targeting of venous capacity may improve acute management of hypertension.

P.13 - Sex-specific Autonomic Dysregulation Of Cardiovascular And Ventilatory Functions Following Acute Irreversible Acetylcholinesterase Inhibition

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Introduction: Acute exposure to organophosphate pesticides, such as chlorpyrifos (CPF), leads to the irreversible inhibition of acetylcholinesterase (AChE), triggering a cholinergic crisis. While CPF neurotoxicity is well-known, the influence of sex as a biological variable on the autonomic control of cardiovascular and ventilatory homeostatic parameters remains poorly understood.

Methods: Male and female Wistar rats (n = 7-12 /group) received CPF (30 mg/kg, i.p.) or saline. After 24h, ventilatory variables (VT, VE, and fR) were recorded by whole-body plethysmography. Hemodynamic parameters (MAP and HR) were then monitored via a catheterized femoral artery. After recordings, blood samples were collected to assess plasma butyrylcholinesterase (BuChE) activity using the Ellman´s method. Data were analyzed by two-way ANOVA with Tukey's post-hoc (CEUA Nº 04/2024 and 17/2022).

Results: Acute CPF exposure was confirmed by a significant reduction in BuChE activity in both males (± 84.07%) and females (± 85.19%). Irreversible inhibition induced distinct sex-specific profiles: intoxicated males exhibited a significant reduction in tidal volume (VT: 1.14 ± 0.41 vs. control: 3.38 ± 0.41 mL.kg-1) and minute ventilation (VE: 138.3 ± 53.86 vs. control: 336.5 ± 53.86 mL.kg-1.min-1), with no changes in HR. Conversely, intoxicated females showed significant bradycardia (HR: 317.8 ± 20.75 vs. control: 344.0 ± 20.75 bpm) without ventilatory alterations. MAP and fR remained stable across all groups.

Conclusion: Our findings demonstrate that CPF-induced autonomic dysfunction is sex-dependent. While males are more susceptible to ventilatory mechanics impairment, females exhibit a selective vulnerability to cardiac chronotropic dysregulation. These results underscore the importance of sex-specific analysis in the physiological failure following autonomic chemical challenges.

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P.14 - Hpa Axis Modulation Of Behavioral, Cardiovascular, And Neuroendocrine Responses To Social Defeat Stress In Rats

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INTRODUCTION: Social defeat model induces defensive behaviors in submissive rats, triggering behavioral, autonomic, and endocrine responses, notably involving activation of the hypothalamus-pituitary adrenal (HPA) axis. The HPA axis plays a central role in coordinating stress-related responses by regulating the release of glucocorticoids. METHODS: Experimental procedures were approved by the Animal Experimentation Ethics Committee of the University of São Paulo (protocol 1352/2024). Male Wistar rats received either prednisolone (5 mg/kg, i.p.) for 14 days or a single dose of metyrapone (200 mg/kg, i.p.) to investigate the role of the HPA axis in social defeat stress. Body weight and food intake were monitored throughout treatments and stress protocols. Animals were exposed to seven days of social defeat using the resident-intruder model. Behavioral (Splash Test and Novel Object Recognition), cardiovascular (mean arterial pressure and heart rate), and neuroendocrine (plasma ACTH and corticosterone) parameters were evaluated. Data were analyzed using two-way ANOVA. RESULTS: Prednisolone reduced plasma ACTH ($F_{1,21}$ = 28.39, $p < 0.0001$) and corticosterone ($F_{1,18}$ = 22.63, p = 0.0002), whereas metyrapone increased ACTH ($F_{1,19}$ = 13.80, p = 0.0015) and corticosterone ($F_{1,19}$ = 13.80, p = 0.0015). HPA axis suppression reduced body weight gain ($F_{3,85}$ = 21.84, $p < 0.0001$) and food intake ($F_{1,26}$ = 323.7, $p < 0.0001$), whereas HPA axis hyperactivation increased food intake without affecting body weight. Social defeat reduced grooming time ($F_{1,64}$ = 28.55, $p < 0.0001$). HPA axis suppression did not reverse this effect, whereas HPA axis hyperactivation increased grooming time ($F_{1,40}$ = 4.82, p = 0.0338). Social stress impaired long-term memory, which was not prevented by HPA axis suppression. In contrast, HPA axis hyperactivation improved short-term ($F_{1,49}$ = 4.83, p = 0.0327) and long-term memory ($F_{1,49}$ = 6.27, p = 0.0156). HPA axis suppression increased MAP in stressed animals ($F_{1,45}$ = 6.40, p = 0.0149), whereas HPA axis hyperactivation didn´t alter cardiovascular parameters.

CONCLUSION: These findings demonstrate that HPA axis suppression and HPA axis hyperactivation differentially modulate behavioral, cognitive, neuroendocrine and cardiovascular responses to social defeat. Overall, preserved HPA axis activity appears protective during chronic social stress, whereas HPA axis suppression contributes to maladaptive stress responses.

P.15 - Delta Heart Rate Poorly Reflects Symptom Burden In Postural Orthostatic Tachycardia Syndrome

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Introduction: Delta heart rate during an orthostatic challenge test of ≥30bpm, in addition to an unexplained postural symptom burden, is central to the diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS) in adults and is frequently used as an outcome measure in clinical research. However, it remains unclear if delta heart rate is reflective of autonomic symptom burden, fatigue severity, or quality of life.

Methods: A cross-sectional analysis was conducted in 218 consecutive participants enrolled in the Australian POTS Registry between May 2021 and January 2024. All participants had physician-confirmed POTS according to standardised international diagnostic criteria. Delta heart rate was measured using a standardised Active Stand Test prior to clinical review. Participants completed validated patient-reported outcome measures (PROMs), including the Composite Autonomic Symptom Score-31 (COMPASS-31), Malmö POTS Score, Fatigue Severity Scale (FSS), and EuroQol-5D-5L (EQ-5D-5L). Associations between delta heart rate and PROMs were assessed using Spearman's rank correlation.

Results: The cohort had a mean age of 31.2±12.0 years; 89.4% were female and 98.7% were White. Mean delta heart rate was 37±3.6 beats/min. Mean COMPASS-31 score was 49.9±14.2 and mean Malmö POTS score was 68.2±22.1, indicating substantial autonomic symptom burden. Delta heart rate was not associated with autonomic symptom burden measured by COMPASS-31 ($r=-0.053$, $p=0.44$) or Malmö POTS score ($r=-0.074$, $p=0.28$). No significant associations were observed with fatigue severity ($r=0.02$, $p=0.77$), EQ-5D-5L visual analogue scale ($r=0.04$, $p=0.95$), or utility score ($r=0.05$, $p=0.46$).

Conclusion: Delta heart rate was not associated with autonomic symptom burden, fatigue severity, or health-related quality of life in this cohort. While delta heart rate is currently central to the diagnosis of POTS, it appears to be a poor marker of symptom severity. Additional clinical and biological markers are needed to better assess symptom burden and guide treatment. In individuals with substantial symptoms despite a negative orthostatic challenge test, repeat testing and further clinical evaluation and treatment should be considered.

P.16 - Selected Parameters Of Autonomic Modulation Of Blood Circulation In Parkinson's Disease

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Introduction: Homeostasis of the circulatory system is based on reflex control mechanisms mediated by the sympathetic and parasympathetic divisions of the autonomic nervous system. Dysfunction of the autonomic nervous system is common in Parkinson's disease

Objective: An assessment of selected functional parameters of the autonomic nervous system involved in the regulation of blood circulation in individuals with Parkinson's disease.
Methods: Study group PA: 20 patients with Parkinson's disease, median age 62.0 years, 12 men, Study group CO: 30 control person subjective heatlhy, median age 54.7 years, 10 men
Investigation protocol was approved by the local ethics committee. Spectral analysis of heart rate variability (HRV) measures: LF (low frequency component), HF (high frequency component): 5-minute ecg in supine position after 5 min orthostatic chalenge, sinus rhythm after filtration of artefacts and extrabeats (microcomputer system type DiANS PF 8).
Baroreflex effectivity index (BEI): continuous blood pressure recording during 5-minute tilt to 65 degrees (Task Force Monitor). Handgrip (HGRIP): continuous blood pressure recording during 30 % maximal contraction for 3 minutes (Finapres) Reactive hyperaemia index (RHI): the assessment of peripheral arterial tone following a 5-minute occlusion was examined using the EndoPat system with finger sensors to evaluate endothelial function. ECG were performed to verify sinus rhythm (Itamar). Statistics: Mann-Whitney U test, chi square test, Shapiro-Wilkov test

Results: No significant differences were found in terms of age (p 0.175) or gender (p 0.525) between the Parkinson's group (PA) and the control group (CO).
Median values Group PA / Group CO
Power LF (ms2): 94 / 328 (p 0.009)
Power HF (ms2): 151 / 255 (p 0.015)
BEI: 37.3 / 54.1 (p 0.020)
HGRIP (mm Hg): 18.0 / 27.0 (p 0.007)
RHI: 1.38 0 1.65 (p 0.005)

Conclusions: In patients with Parkinson's disease, we observed statistically significant abnormalities in the autonomic regulation of heart rate (HRV) and blood pressure (BEI, HGRIP), as well as the presence of endothelial dysfunction (RHI). The findings indicate to hemodynamic consequences of dysautonomia.

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P.17 - Clinical Evidence Of Early And Progressive Cardiovascular Autonomic Dysfunction In Type 1 Diabetes

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Background: Individuals with type 1 diabetes (T1D) have markedly greater cardiovascular disease (CVD) risk, particularly with aging and microvascular disease (MVD). Although autonomic dysfunction is recognized in advanced diabetes, differences between older adults with and without long standing T1D remain incompletely characterized, and it is unknown whether autonomic impairments are present in young adults with T1D.
Purpose: To compare clinical autonomic function between older adults with and without long-standing T1D and determine whether young adults with T1D also demonstrate autonomic impairments.

Methods: Older adults with (N=27, 67±7 years) and without (N=26, 62±8 years) long-standing T1D (~49 years) and young adults with (N=8, 24±3 years) and without (N=5, 26±3 years) T1D completed autonomic testing: Valsalva's maneuver, 60° head-up tilt, 3-minute sustained isometric handgrip (30% of maximum voluntary contraction), and 5-minute resting heart rate variability (HRV). Outcomes included Valsalva ratio (VR), systolic blood pressure (SBP) response to tilt, 30:15 tilt ratio, diastolic blood pressure response to handgrip, mean R-R interval (mRRI), and HRV measures including RMSSD, SDNN, and low- and high-frequency (LF and HF) power. Group differences were assessed using two-sample t-tests, with post hoc analyses accounting for CVD and MVD in the older cohort.
Results: Compared to older controls, older adults with T1D demonstrated shorter mRRI (946±117 vs. 1055±118 ms, p=0.002), lower SDNN(3.48 ± 0.58 vs. 3.80 ± 0.48, p=0.04), LF (5.16 ± 1.60 vs. 5.97 ± 1.14, p=0.04), and VR (1.42±0.20 vs. 1.78±0.30, p<0.001). Young T1D adults showed similar trends, including shorter mRRI (850±82 vs. 1020±173 ms, p=0.09), lower SDNN(3.73 ± 0.37 vs. 4.04 ± 0.47, p=0.24), and VR (1.64±0.12 vs. 1.95±0.26, p=0.05), indicating a cardiovagal deficit progressing with age. Older adults with T1D had greater orthostatic SBP declines than controls (-12.9±12.3 vs. -5.4±9.4 mmHg, p=0.02), with similar trends in the young cohort, indicating impaired blood pressure regulation. Among older adults with T1D, those with MVD had greater orthostatic SBP reductions than those without MVD (-16.2±12.9 vs. -5.3±6.3 mmHg; p=0.007).

Conclusion: Autonomic dysfunction may emerge before substantial CVD burden in T1D, supporting further study of autonomic mechanisms underlying elevated CVD risk in T1D.
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P.18 - Ambulatory Blood Pressure Monitoring In Persons With Spinal Cord Injury

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Introduction: Cardiovascular disease is one of the leading causes of morbidity and mortality in the spinal cord injury (SCI) population. Ambulatory BP monitoring (ABPM) provides the average BP, circadian rhythm, and short-term BP variability. Blood pressure values are classified into diurnal (06:30-22:00) and nocturnal (22:00-06:30) periods.

Methods: We perform a 24-hour AMBP on patients admitted to the Spinal Cord Injury Centre of Western Denmark for primary rehabilitation in 2025.

Results: We obtained a complete 24-hour AMBP from 88 patients, 29 women and 59 men. Mean age 57,0 years; women 55,4 years and men 57,9 years. Trauma was the cause of SCI in 44%. More women than men had cervical injury, 59% versus 51%. Only 16% were complete injuries. Mean blood pressure (BP) was 118/71 mmHg in patients with cervical injuries, mean heart rate (HR) 70/min. Mean BP in thoracic injuries 121/72 mmHg, mean HR 75/min. Mean BP in lumbar injuries 115/68 mmHg, mean HR 66 /min.

The dipping phenomenon is a physiological drop in blood pressure during sleep and represents an event related to the circadian blood pressure trend. We divided the patients according to dipper (10-20%), extreme dipper (>20%), non-dipper (0-10%) and revers dipper. In total, 19% were dippers, 2% extreme dipper, 4% non-dipper and 38% revers dipper.

Studies have found a link between obstructive sleep apnoea and reverse dip. CPAP is shown to improve sleep pattern in normotensive able-body individuals.

Conclusions: AMBP is a useful tool in assessing persons with SCI in preventing cardiovascular disease and possible sleep apnoea. Some of our patients had CPAP prior to injury but did not use it. Other patients were found to have sleep apnoea after investigation triggered by their blood pressure profile.

Studies are needed to explore the effect of CPAP on blood pressure in this patient group.

P.19 - Feasibility Of Proteomic Profiling Of Plp1-tdtomato-positive Glial Cells From The Heart

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Introduction: Cardiac glia cells are a rare cell population in the heart whose roles and molecular pathways are still not well described despite emerging evidence connecting them to different neuronal functions. To address this gap, we utilized genetic labeling of glial cells to establish a workflow for their isolation from the mouse heart and subsequent proteome analysis.

Methods: TdTomato-positive (tdT+) cells were isolated from PLP1-CreERT2-tdTomato mice (n=5) by enzymatic digestion and mechanical dissociation, followed by enrichment through filtration and centrifugation steps. TdT+ cells were purified using fluorescence-activated cell sorting (FACS, 100 µm nozzle, purity sort) with exclusion of doublets and DAPI+ events to ensure a viable single-cell population. Non-glial cardiac cells from the same suspension and sciatic nerve tissue served as negative and positive control reference samples, respectively. Purified cells were subjected to quantitative proteomic analysis.

Results: FACS sorting yielded 21,493 ± 9,863 tdT+ cells per heart with 46.5 ± 7.2 % viability, representing 1.2 ± 1.0 % of total non-myocytic cardiac cells. The yield and purity were consistent across biological replicates, confirming the reproducibility of the isolation procedure. The tdT+ population displayed distinct forward and side scatter characteristics, revealing a subpopulation and indicating cellular heterogeneity. Proteomic profiling identified 2,344 protein groups detected in the cardiac tdT+ cell group. Principal component analysis separated the groups into distinguishable clusters, while technical replicates showed intragroup correlations. Data completeness was highest in the positive control group (55.2 %) and lowest in the tdT+ cell group (12.5 %).

Conclusion: Our study established a feasible workflow for isolating and characterizing proteins of cardiac glial cells. Although input material was limited, as expected for a rare cell population, data quality was sufficient for downstream analyses. Taken together, this approach provides a foundation for future investigations into the molecular mechanisms and functional roles of cardiac glia.

P.20 - Changes In Cardiovascular And Hypothalamic Neural Excitability Responses In Dominant Animals During Social Defeat Stress

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Harassment in schools and workplaces is a major social problem, as psychological stress in victims can lead to mental disorders such as depression and anxiety. In addition, harassment-induced stress can contribute to cardiovascular dysfunction, including hypertension and palpitations, through autonomic imbalance, thereby impairing quality of life. The social defeat stress (SDS) model is widely used to study harassment-related stress in animals; however, most studies have focused on defeated individuals, examining depressive-like behaviors and physiological changes. To better understand harassment as a social issue, it is also important to investigate the responses of dominant individuals who inflict stress, although these remain largely unexplored.

In this study, Wistar rats were used as the defeated group and Long-Evans (LE) rats as the dominant group. Cardiovascular responses and central neural activation in dominant rats were compared with those in non-experienced controls. During a 10-minute confrontation with a Wistar rat, LE dominant rats were classified as aggressive or non-aggressive based on their behavior, and differences in stress-related physiological and neural responses were analyzed.
In the aggressive group, mean blood pressure (MBP) and heart rate (HR) increased immediately after SDS onset and returned to baseline before the end of the stress period. In contrast, in the non-aggressive group, MBP and HR also increased but remained elevated throughout the stress period, suggesting that these animals experienced greater stress. However, this difference was not reflected in neural activity within stress-related centers, the dorsomedial hypothalamus (DMH). Although c-Fos expression in neurons in the DMH increased in both LE dominant groups, the number of c-Fos–immunoreactive neurons was significantly higher in the aggressive group. This discrepancy between cardiovascular responses and hypothalamic activation remains unresolved and suggests that DMH neurons may contribute not only to stress-induced cardiovascular regulation but also preferentially to behavioral outputs such as aggression.

P.21 - Thoracoscopic Bilateral Sympathectomy For Medically Refractory Vasospastic Angina

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Introduction: Vasospastic angina (VSA) is generally managed with calcium channel blockers and vasodilators. However, a subset of patients continues to experience recurrent angina, ventricular arrhythmias, syncope, or aborted sudden cardiac death despite maximal medical therapy. In these medically refractory cases, treatment options remain limited. Thoracoscopic cardiac sympathectomy has emerged as a potential rescue therapy by reducing sympathetic-mediated coronary vasoconstriction and arrhythmogenic triggers.

Methods: We retrospectively reviewed the medical records of patients with medically refractory VSA who underwent thoracoscopic bilateral sympathectomy between February 2026 and December 2026. The procedure was performed using a 5-mm thoracoscope, with resection of the third and fourth thoracic sympathetic ganglia. The right-sided sympathectomy was performed first. If no significant bradycardia or arrhythmia occurred following right-sided resection, the procedure was completed on the left side.

Results: Three female patients with medically refractory VSA underwent thoracoscopic bilateral sympathectomy. One patient had recurrent ventricular fibrillation and multiple appropriate implantable cardioverter-defibrillator (ICD) shocks despite maximal medical therapy. The second patient experienced severe medication-related hypotension that precluded adequate symptom control. The third patient suffered from persistent angina that significantly impaired daily activities and professional performance despite optimal pharmacologic treatment. Following thoracoscopic bilateral sympathectomy, all patients experienced marked improvement in anginal symptoms with a reduction in medication requirements. No recurrent ventricular fibrillation, cardiac arrest, or hospitalization due to refractory angina occurred during follow-up. All patients remain clinically stable in the outpatient setting.

Conclusions: Thoracoscopic bilateral sympathectomy may represent a safe and effective therapeutic option for carefully selected patients with medically refractory VSA. This approach may be particularly beneficial in patients with malignant ventricular arrhythmias, intolerance to intensive vasodilator therapy, or persistent disabling symptoms despite maximal medical treatment.

P.22 - Adding Carbon Dioxide To Acute Intermittent Hypoxia Potentiates Sympathetic Long-term Facilitation In Rodents With High-thoracic Spinal Cord Injury

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Introduction: Disruption of descending medullary signaling to spinal sympathetic circuits contributes to hemodynamic instability and elevated cardiovascular disease risk after high-level spinal cord injury (SCI). Therefore, identifying strategies to modulate sympathetic outflow is critical. Acute intermittent hypoxia (AIH) can induce long-term facilitation (LTF), a sustained increase in neural activity after repeated hypoxic exposure. In motor systems, LTF can be augmented by pairing hypoxia with elevated CO_2, termed acute intermittent hypercapnic hypoxia (AIHH). However, whether AIHH enhances sympathetic LTF (sLTF) compared with AIH alone after SCI remains unknown. Methods: Sixteen male Wistar rats underwent severe T2/3 contusion SCI (300 kdyn). Four weeks later, rats were anaesthetized and instrumented for measurement of arterial blood pressure, superior mesenteric artery flow (QSMA), and splanchnic sympathetic nerve activity (sSNA). Following baseline recordings, rats were randomly assigned to a single session of AIHH or AIH. AIHH consisted of 10 × 1-min exposures to FiO_2 = 0.10 and $FiCO_2$ = 0.06, balanced in N_2, interspersed with 2-min exposures to FiO_2 = 0.28. AIH consisted of 10 × 1-min exposures to FiO_2 = 0.10, balanced in N_2, interspersed with 2-min exposures to FiO_2 = 0.28. Outcomes were compared at 1, 30, and 60 min post-intervention. Results: Both AIH and AIHH elicit splanchnic sLTF following SCI ($p = 0.048$ and $p = 0.0063$, respectively), with a greater response after AIHH compared with AIH (1.86 ± 1.28 μV vs. 0.55 ± 0.27 μV, $p = 0.016$). Enhanced sLTF appears to be primarily associated with increased burst peak area ($p = 0.0005$). In contrast, burst frequency, burst incidence, burst width, and burst-size distribution remained unchanged at 1, 30, and 60 min after AIHH. Burst-size distribution was assessed by classifying detected bursts into three size-based clusters using k-means clustering; the relative distribution across clusters did not change over time. Although blood pressure decreased in both AIHH and AIH groups ($p < 0.0001$ and $p = 0.0015$, respectively), QSMA and CSMA remained stable following AIHH. Conclusion: These findings suggest that AIHH may enhance splanchnic sLTF after SCI and support further investigation of chronic AIHH-based interventions to mitigate cardiovascular dysfunction associated with sympathetic hypoactivity.

P.23 - On The Hemodynamic Response To Exercise In Parkinson's Disease: Does Neurogenic Orthostatic Hypotension Matter?

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Parkinson's disease is a neurodegenerative disorder characterized by both motor and non-motor symptoms. Cardiovascular autonomic dysfunction is a major non-motor manifestation that affects about half of people with Parkinson's disease and may present as neurogenic orthostatic hypotension (OH). However, cardiovascular responses to exercise in Parkinson's disease remain poorly characterized, particularly in patients with vs. without OH. Therefore, this study aimed to compare central and peripheral hemodynamic responses to exercise in people with Parkinson's disease with OH (PD-OH), without OH (PD), and healthy controls (CTRL).

Five PD (67±10 years), 4 PD-OH (73±6 years), and 7 matched CTRL (64±4 years) participated in the study. Both patient groups remained on their usual carbidopa/levodopa treatment. Participants performed an incremental single-leg knee-extension test with 5W (males) or 3W (females) increases every 2 minutes. Leg blood flow (LBF) was measured by Doppler ultrasound during the second minute of each stage. Mean arterial pressure (MAP) and cardiac output (CO) were continuously measured by finger photoplethysmography and averaged over the final minute of each stage. Leg vascular conductance (LVC) and systemic vascular conductance (SVC) were calculated as LBF/MAP and CO/MAP, respectively. Linear mixed-models quantified the slopes of each variable relative to absolute work rate.

Baseline cardiovascular variables did not differ between groups (all $P>0.27$). Peak work rates were 41±17 W in CTRL, 34±16 W in PD, and 27±14 W in PD-OH. During exercise, the MAP slope differed in PD-OH compared with CTRL and PD (both $P<0.01$), whereas CTRL and PD were not different ($P=0.13$). Notably, MAP did not significantly increase with work rate in PD-OH. LBF, LVC, and SVC increased with work rate in all groups. Their slopes were similar between CTRL and PD (all $P\geq0.44$) but significantly greater in PD-OH (all $P<0.02$). CO responses did not differ between groups ($P>0.10$).

Abnormal cardiovascular responses to exercise in Parkinson's disease appear specific to the presence of autonomic dysfunction rather than Parkinson's disease itself. Whereas PD showed hemodynamic responses similar to CTRL, PD-OH exhibited a marked pressor deficit despite preserved CO responses. This impairment appears to reflect exaggerated peripheral and systemic vasodilation, consistent with reduced sympathetic vasoconstrictor restraint during exercise.

P.24 - Effect Of Involuntary Breathing Movements On Aortic Flow

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Introduction: Prolonged apnea results in hypoxaemia and hypercapnia. The body responds by centralising flow to vital organs. Initially, respiratory muscles are immobile, but, as hypoxaemia and hypercapnia worsen, the initial physiological response becomes insufficient, and involuntary breathing movements (IBMs) occur. These movements appear to improve cerebral oxygenation by increasing venous return. However, the precise effects of IBMs on blood flow changes have not been accurately quantified yet.

Methods: We used real-time MRI to measure blood flow in the ascending and descending aorta of seven experienced apnea divers (1 woman, 47 ± 8 years, 23.1 ± 0.7 kg/m2). Blood flow was measured at baseline, in the first apnoeic phase, characterised by absence of IBMs, at the beginning, middle and end of the second apnoeic phase with IBMs, and during recovery.

Results: Compared to baseline, left ventricular stroke volume decreased to 55 % in the first apnoeic phase and gradually recovered during IBMs (67, 85 and 99 %) with a slight overshoot during recovery (115 %). Flow in the descending aorta showed a similar response, with an attenuated recovery during IBMs (55 % in the first apnoeic phase; 64, 70 and 78 % during IBMs; 103 % during recovery). The increase in stroke volume was accompanied by a slight decrease in heart rate, and a significant increase in brachial blood pressure and blood pressure amplitude during IBMs (158/94 vs. 128/74 mmHg at baseline). Peripheral oxygen saturation decreased from 90 % at the beginning of IBMs to 72 % slightly after the end of apnea.

Conclusion: Our findings suggest that involuntary breathing movements improve cardiac output, becoming more effective with time. Therefore, together with increased peripheral resistance, IBMs help maintain stroke volume and hence cerebral oxygenation during apnea.

P.25 - Cardioprotection Through A Brain-gut-heart Axis: Glp-1r/katp Signalling In Cardiac Pericytes Prevents Coronary No-reflow

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Introduction. After reopening a blocked coronary artery, up to 50% of patients with myocardial infarction experience microvascular "no-reflow", resulting in larger infarcts and increased mortality. We previously demonstrated that no-reflow is caused by cardiac pericyte-mediated capillary constriction and that remote ischaemic preconditioning (RPc) and vagus nerve stimulation protect the heart via the release of the gut hormone GLP-1. Here, we aimed to define the molecular mechanisms downstream of GLP-1R activation involved in the prevention of no-reflow.

Methods and results. Using in vivo ischaemia/reperfusion (IR) models in rats and mice and ex vivo live cardiac tissue imaging, we investigated GLP-1R signalling in cardiac pericytes. RPc markedly reduced pericyte-mediated capillary constriction and no-reflow (11.4±0.4% reduction in coronary perfusion in IR+RPc vs 40.8±0.5% in IR; p=0.004). This protection was abolished by the GLP-1R antagonist Exendin(9-39) (28.7±0.8% vs 11.4±0.4%; p=0.013). Oxygen-glucose deprivation induced robust pericyte contraction ex vivo (15.9±1.7% capillary constriction), which was rapidly reversed by the GLP-1R agonist Exendin-4 (5.0±1.1%; p<0.0001). GLP-1R-mediated pericyte relaxation required opening of KATP channels: deletion of Kir6.1 subunit of KATP channels in pericytes prevented relaxation (21.4±1.1% constriction, p<0.0001) and abolished RPc-induced infarct size reduction in vivo (29.0±2.8% in the KO IR+RPc group vs 10.0±1.0% in the WT IR+RPc group; p=0.0002). Inhibition of AMPK, NO synthase or muscarinic signalling also prevented GLP-1R-dependent pericyte relaxation, and AMPK inhibition promoted KATP channel internalisation in vivo. This suggests that the coronary blood flow increase and cardiac protection by RPc may be modulated by agents that alter the membrane trafficking of KATP channels.

Conclusions. These findings define a brain-gut-heart pathway whereby vagal activity and RPc promote GLP-1 release to protect the ischaemic heart by targeting pericyte KATP channels. GLP-1R agonists and KATP channel modulators represent promising therapies to prevent no-reflow and improve post-infarct outcomes.

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P.26 - In Situ Cholinergic Overstimulation Differentially Disrupts Cardiovascular Reflex Control In Normotensive And Pre-hypertensive Rats

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The cholinergic system plays a central role mediating both parasympathetic and sympathetic ganglionic transmission and its dysregulation contributes to pathologies such as hypertension. Cholinergic overstimulation, such as that observed during organophosphate (OP) poisoning, induces autonomic imbalance that can lead to severe cardiovascular disturbances and cardiorespiratory failure. We previously showed that chlorpyrifos (CPF), a commonly used OP, impairs cardiorespiratory reflexes in normotensive rats and increases mortality in SHR. Therefore, using acute OP-induced as cholinergic overactivation model, we aimed investigated whether pre-hypertensive rats already display altered cardiovascular reflex responses compared with normotensive animals.

Using the working heart-brainstem preparation, we recorded heart rate, phrenic nerve activity, and thoracic sympathetic nerve activity in both Wistar and pre-hypertensive SHR (4-5 week old; CEUA 17/2022). Baroreflex, chemoreflex and Bezold–Jarisch reflex (BJR) were evoked by phenylephrine, potassium cyanide and phenylbiguanide, respectively, before and after chlorpyrifos-oxon (CPO; 15 mg/kg). Cholinesterase activity was measured in the brainstem. Data were analyzed using two-way ANOVA and generalized mixed models (n = 10/group).

CPO differentially modulated cardiovascular reflexes in normotensive and pre-hypertensive rats. Baroreflex bradycardic gain was attenuated in Wistar rats (Δ = +27.5 bpm/mmHg·s^{-1}) but reduced in SHR (Δ = −4.9 bpm/mmHg·s^{-1}; $p < 0.05$), indicating opposite strain-dependent effects. Sympathetic baroreflex gain was unchanged after CPO, although reduced by DMSO in SHR. CPO also impaired the chemoreflex, reducing sympathetic responses (~14%) while enhancing bradycardia (~31%) similarly in both strains, but produced opposite respiratory effects, inhibiting tachypnea in Wistar and enhancing it in SHR. In BJR, CPO increased the bradycardic response (~40%) and reduced perfusion pressure (~30%) in both strains, while attenuating sympathoinhibition, with a greater effect in SHR. Respiratory responses were altered, with attenuation of bradypnea and a selective prolongation of expiratory time in Wistar rats. Brainstem cholinesterase activity was markedly inhibited (~90%) in both strains. Our findings show that cholinergic overstimulation impairs cardiorespiratory integration, with differential effects between hypertensive and normotensive phenotypes. Strain-specific vulnerabilities may influence clinical outcomes and highlight the importance of autonomic phenotype in OP toxicity.

Keywords: organophosphate poisoning, cardiovascular reflexes, hypertension.

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P.27 - The Role Of Oxytocin Within The Rostral Ventrolateral Medulla In The Tonic And Reflex Regulation Of Blood Pressure In An Animal Model Of Polycystic Kidney Disease

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Introduction: The rostral ventrolateral medulla (RVLM) is a key cardiovascular centre in the baroreflex pathway, driven by excitatory input from the paraventricular nucleus (PVN). In the Lewis Polycystic Kidney (LPK) rat model of polycystic kidney disease (PKD), neurogenic hypertension and baroreflex dysfunction are linked to overactive PVN vasopressin neurons. The contribution of PVN oxytocin overactivity remains unclear, particularly at the RVLM. This study examines whether oxytocin signaling in the RVLM contributes to hypertension and baroreflex resetting in male and female LPK rats.

Methods: Basal PVN activity across sex, strain, and PKD status was assessed using FosL-1 expression with oxytocin (OXT) and vasopressin (AVP) immunohistochemistry. In anaesthetised male and female Lewis and LPK rats, systolic blood pressure (SBP), heart rate (HR), and HR baroreflex sensitivity were recorded following RVLM microinjection of oxytocin, an oxytocin receptor (OXTR) antagonist (L-368 899), or a vasopressin receptor 1a (V1aR) antagonist (SR49059). RNAscope with DAPI staining was used to examine OXTR and V1aR localisation in the RVLM.

Results: Female Lewis and male LPK rats showed increased AVP(+)/FosL-1(+) and OXT(+)/FosL-1(+) neurons compared to male Lewis controls, while female LPK rats showed no differences. Oxytocin increased HR and SBP in all groups, with significant sex- and strain-dependent HR responses. In male LPK rats, oxytocin reduced HR baroreflex range. OXTR blockade (L-368 899) induced tachycardia and increased SBP in all groups, with greater responses in male LPK rats, suggesting enhanced OXTR pathway activity. V1aR blockade (SR49059) pressor responses in LPK rats, indicating a pro-hypertensive role for V1aR. Neither antagonist altered baroreflex sensitivity. RNAscope showed OXTR and V1aR are largely expressed on separate RVLM cells, significantly so in male LPK rats, with minimal colocalisation and no overall expression differences between groups.

Conclusion: OXTR and V1aR are distributed throughout the RVLM and exhibit opposing cardiovascular roles, with OXTR appearing anti-hypertensive and V1aR pro-hypertensive. Enhanced OXTR pathway activity in male LPK rats may represent a compensatory response to neurogenic hypertension rather than a causative factor.

P.28 - Chronotropic Incompetency At The Onset Of Volitional Handgrip Exercise In Individuals With Drug-resistant Epilepsy

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Introduction: The rapid cardiovascular response to brief, volitional isometric handgrip exercise involves cardiovagal withdrawal that, in turn, associates with modified activity patterns within the central autonomic network (CAN). Drug-resistant epilepsy (DRE) is characterized by disordered cortical behaviour in primary epileptogenic sites that overlap CAN regions. We tested the hypothesis that the typical cardiac responses to volitional handgrip exercise would be impaired by DRE as evidence of altered brain-heart integration.

Methods: We compared heart rate (HR) reactivity to isometric handgrip (40% maximal strength) in cohorts of healthy controls (n=42; 24M/18F; age: 24±7 years) and individuals with DRE (n=33, 18M/15F; Age 36±11). Participants performed a series of 20-second HG at 40% of maximal volitional strength and Borg scale reports of Control=13.1±2.0 and DRE=12.5±1.9 units of perceived exertion. Physiological metrics were quantified at baseline and during 10–20 seconds following handgrip onset. HR was calculated from the electrocardiogram and Mean Arterial Pressure (MAP) was measured using finger photoplethysmography (Finometer). Changes in vagal cardiac function were assessed using the root mean square of successive differences (RMSSD).

Results: Compared to baseline, the cardiovascular changes in Control cohort were ΔHR = 8.24 ± 6.83 bpm ($p < 0.001$), ΔRMSSD= -26±24 ms ($p<0.001$), and ΔMAP=4.94±6.03 mmHg ($p<0.001$). Conversely, the DRE cohort exhibited lower baseline RMSSD versus Controls ($p=0.033$) and, compared to baseline, the cardiovascular responses to handgrip were ΔHR=1.6±5.0 bpm ($p =0.072$), ΔRMSSD= -3.49±14 ms ($p=0.161$) and ΔMAP=4.5±5.3 mmHg ($p<0.001$). Compared to Control the ΔHR and ΔRMSSD were less in DRE (both $p<0.001$) whereas the ΔMAP with was not different between groups ($p=0.75$). Neither baseline HR or MAP predicted handgrip-induced ΔHR (Control: $R^2=0.01$, $p=0.55$; DRE: $R^2=0.11$, $p=0.05$) or ΔMAP (Control: $R^2<0.01$, $p=0.64$; DRE: $R^2=0.06$, $p=0.23$) but baseline RMSSD did predict the ΔRMSSD with handgrip in Controls ($R^2=0.54$, $p<0.001$) and less so in DRE ($R^2=0.16$, $p=0.023$).

Conclusion: Despite the normal MAP response, the expected reduction in RMSSD and increase in HR with handgrip was not observed in DRE. These findings suggest a dysregulation in the brain-heart axis in DRE that may be related to disrupted CAN properties.

P.29 - Beyond The Tilt Table Test: Resting Hrv Analysis For Non-invasive Detection Of Cardiovascular Dysautonomia

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Autonomic nervous system (ANS) dysfunction, or dysautonomia, refers to a heterogeneous spectrum of conditions characterized by impaired cardiovascular autonomic regulation, including orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS), and vasovagal syncope (VVS) [1]. The tilt table test (TTT) is the gold standard for diagnosing dysautonomia; however, it is time-consuming, resource-intensive, and not universally accessible [2]. Heart rate variability (HRV) analysis of resting ECG recordings represents a non-invasive and cost-effective alternative for assessing autonomic function. The aim of this study is to evaluate which HRV biomarkers, derived from short resting ECG recordings, are capable of discriminating dysautonomia from normality. A total of 70 subjects were enrolled in this retrospective study: 35 healthy controls and 35 dysautonomic individuals classified based on TTT outcome, comprising 36 males and 34 females (mean age 45.0 ± 20.4 years; range 13–86). Recordings of 3 to 5 minutes were analysed to extract time-domain (SDNN, RMSSD, pNN50), frequency-domain (LF, HF, LF/HF ratio) and non-linear HRV indices (SD1, SD2, DFA α1, SampEn) [3]. Group differences were assessed using Student's t-test or Mann-Whitney U test, with normality verified via the Shapiro-Wilk test, and corrected for multiple comparisons via the Benjamini-Hochberg FDR method [4]. Effect sizes were quantified using Cohen's d [5]. Six HRV features were significantly different between groups after FDR correction ($p < 0.05$): SDNN, RMSSD, pNN50, LF, SD1, and SD2. The most discriminant were SD2 ($d = -0.782$) and SDNN ($d = -0.750$), both reflecting global long-term HRV and significantly reduced in dysautonomic subjects, consistent with a generalized reduction in cardiac autonomic modulation. The remaining significant features showed smaller effect sizes (d ranging from −0.494 to −0.473). DFA α1 ($d = -0.423$) and HF ($d = +0.417$) did not reach statistical significance, which may reflect greater inter-individual variability in these autonomic indices across dysautonomic subtypes rather than a true absence of alteration. These findings support resting HRV indices, particularly long-term variability, as markers of dysautonomia. The predominance of indices over short-term or vagally-mediated features is consistent with a mixed population including POTS, VVS, and OH. Larger studies with subgroups are needed to confirm these findings.

P.30 - Sex-dependent Lateralization Of Cardiovascular Responses To Aortic Baroreceptor Afferent Stimulation In Spontaneously Hypertensive Rats

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Introduction: Baroreceptor-based neuromodulation therapies have stimulated interest in identifying novel approaches for autonomic regulation of blood pressure. In a preclinical model of genetic hypertension, we recently demonstrated that low-energy electrical activation of aortic baroreceptor afferents elicits clinically relevant reductions in arterial pressure, highlighting the therapeutic potential of this neuromodulation strategy. However, little is known regarding the influence of biological sex on cardiovascular responses to aortic baroreceptor afferent activation. Accordingly, the present study investigated the cardiovascular effects of unilateral left and right aortic depressor nerve (ADN) stimulation in male and female spontaneously hypertensive rats (SHRs).

Methods: Pentobarbital-anesthetized SHRs of either sex (total n = 14) were instrumented for stimulation of the left and right ADN (1–40 Hz, 0.2 ms, 0.4 mA, 20 s) and recording of mean arterial pressure (MAP), heart rate (HR), mesenteric vascular resistance (MVR), and femoral vascular resistance (FVR). Female rats were studied during diestrus to minimize variability associated with the estrous cycle.

Results: ADN stimulation evoked frequency-dependent reductions in MAP, HR, FVR, and MVR in both sexes ($P<0.01$). Male SHRs exhibited higher resting MAP than females (177±7 vs. 141±6 mmHg, $P<0.01$), whereas baseline HR, FVR, and MVR were comparable. Stimulation of the left ADN produced greater reductions in MAP, HR, and FVR in males than females. In contrast, stimulation of the right ADN elicited comparable depressor, bradycardic, and femoral vascular responses between sexes, although females exhibited greater reductions in MVR. In contrast, stimulation of the right ADN elicited comparable depressor, bradycardic, and femoral vascular responses between sexes. Although females exhibited greater reductions in MVR, this did not translate into enhanced depressor responses.

Conclusion: These findings reveal a previously unrecognized lateralization of sex-dependent cardiovascular responses to aortic baroreceptor afferent stimulation, with differences predominantly confined to left-sided activation. Collectively, these data suggest that biological sex influences the central integration of aortic baroreceptor afferent input in hypertension and should be considered in the development and optimization of baroreceptor-based neuromodulation strategies for blood pressure control.

P.31 - Orthostatic Hypertension Is Associated With Greater Limitations In Basic Activities Of Daily Living Among Geriatric Outpatients: A Retrospective Analysis

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INTRODUCTION: Orthostatic hypertension (OHT) is an emerging but incompletely understood risk factor for cardiovascular disease and mortality. Although autonomic dysfunction is believed to play a central role in its pathophysiology, the clinical implications of OHT remain unclear.
AIM: To investigate the association between OHT and limitations in basic activities of daily living (b-ADL) among geriatric outpatients.

METHODS: We conducted a retrospective analysis of geriatric outpatients evaluated at the Geriatric Department of University Hospital Brussels (Jette, Belgium). Demographic characteristics, clinical data, and functional assessments were extracted from medical records. Orthostatic blood pressure (BP) responses were assessed using an active supine-to-stand test, with BP measurements obtained after 5 minutes of supine rest and at 1 and 3 minutes after standing. OHT was defined as an increase in BP of ≥20 mmHg and/or an increase in diastolic BP of ≥10 mmHg upon standing, calculated as the difference between standing and supine BP measurements. b-ADL were assessed using the Katz Index. Linear regression analyses were performed to examine the association between OHT and b-ADL limitations.

RESULTS: A total of 95 geriatric outpatients were included in the analysis (mean age: 82 ± 5 years), of whom 65.3% were female. OHT was present in 28% of participants. In adjusted linear regression analyses, OHT was independently associated with greater limitations in b-ADL (adjusted standardized $\beta = 0.323$, $p = 0.019$). In contrast, orthostatic hypotension was not significantly associated with b-ADL limitations.

CONCLUSION: OHT was independently associated with greater limitations in b-ADL among geriatric outpatients in this retrospective analysis. These findings suggest that OHT may represent a clinically relevant marker of functional vulnerability. Further prospective studies are warranted to clarify the underlying mechanisms and determine whether identification and management of OHT may contribute to preserving functional independence in this population.

P.32 - Increased Pvn To Nts Signaling May Underlie Exaggerated Bezold Jarisch Reflex Bradycardia In A Murine Sudep Model With Stress Hyperreactivity

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Introduction: Sudden unexpected death in epilepsy (SUDEP), the leading cause of death in epilepsy, is characterized by cardiorespiratory failure following a seizure. Emerging evidence implicates reflex activation conveyed by visceral sensory afferents terminating in nucleus of the solitary tract (NTS) as a potential SUDEP trigger. We recently showed that Bezold Jarisch Reflex (BJR), a serotonin type 3 receptor mediated cardiopulmonary reflex causing cardiorespiratory depression, becomes excessive in a mouse model of SUDEP with exaggerated stress responses. Here we hypothesized that increased BJR magnitude occurs through central not peripheral mechanisms with increased PVNCRH signaling to NTS contributing to excessive bradycardia.

Methods: Experiments used mice with hyperactive corticotropin-releasing hormone neurons (Kcc2/Crh), along with genotype controls (Kcc2f/f and Crh/Cre). The ventral intrahippocampal kainate model of temporal lobe epilepsy was employed (vIHKA). To test peripheral contributions to BJR exaggeration, heart rate responses to graded distal vagus nerve stimulation were recorded in urethane anesthetized mice after atenolol administration and bilateral vagotomy. BJR-mediated neuronal activation was accessed via reflex activation with phenylbiguanide (100ug/kg) and quantification of NTS cFos expression. To examine central modulation of BJR, PVNCRH neurons were transduced with AAV1-Ef1a-DIO-ChETA-EYFP in Crh/Cre mice. 4 weeks later, mice were urethane anesthetized and blood pressure (BP) and heart rate (HR) recorded. PVNCRH terminals in NTS were optically activated at baseline and during BJR.

Results: Baseline and intrinsic HR did not differ across groups. Electrical stimulation of the transected right vagus nerve elicited a frequency dependent bradycardia, with no difference between groups. BJR-evoked NTS cFos expression was significantly decreased in epileptic Kcc2/Crh compared to non-epileptic control ($p= 0.0148$). Optical activation of PVNCRH terminals in NTS produced minor and inconsistent effects on resting HR and BP. However, stimulation of PVNCRH terminals in NTS during BJR increased bradycardia ($p= 0.0284$), without altering the depressor response.

Conclusion: Exaggerated BJR bradycardia occurs in epileptic Kcc2/Crh mice through central, not peripheral mechanisms, which is not mediated by overall NTS activation since cFos expression was decreased. However, PVNCRH signaling to NTS increases BJR bradycardia providing a working central circuit-based model of how stress promotes improper weighting of homeostatic reflexes that may increase SUDEP risk.

P.33 - Muscle Sympathetic Nerve Activity Is Elevated In Healthy Pacific Peoples

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Introduction: Cardiovascular disease disproportionately affects Pacific Peoples (PP) (i.e. those originating from Polynesia, Micronesia, and Melanesia) living in New Zealand. The underlying mechanisms are likely complex and multifactorial. Prolonged overactivation of sympathetic nerve activity (SNA) is strongly associated with the onset and progression of cardiovascular disease. Therefore, we sought to make the first measures of sympathetic nerve activity (SNA) in healthy PP and compare these to New Zealand Europeans (NZE).

Methods: In 8 healthy PP (5 women) and 8 healthy NZE (6 women) muscle SNA (microneurography), heart rate (HR, electrocardiogram) and blood pressure (BP, finger photo-plethysmography) were recorded during 10 minutes of supine rest.

Results: PP and NZE had a similar age (28±11 vs. 29±6 yr, P=0.829), height (1.72±0.08 vs. 1.72±0.07 m, P=0.895) and weight (78.0±10.6 vs. 71.0±9.2 kg, P=0.179), respectively. Heart rate (63±7 vs. 66±10 beats/min, P=0.534), systolic BP (120±11 vs. 117±10 mmHg, P=0.649) and diastolic BP (77±7 vs. 70±10 mmHg, P=0.649) were not different between groups. However, PP exhibited higher muscle SNA burst frequency (19±4 vs. 12±5 burst/min, P=0.009) and burst incidence (29±6 vs. 19±11 bursts/100 heartbeats, P=0.039).

Conclusion: These findings show for the first time that compared to NZE, healthy PP have higher levels of directly recorded central sympathetic outflow. Further work is required to determine the potential underlying mechanisms and clinical significance of these important neurogenic differences.

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P.34 - LcPOTS Demonstrates Higher Vagal And Lower Sympathetic Tone Than Classic POTS

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Background: Long COVID–associated postural orthostatic tachycardia syndrome (LCPOTS) has emerged as a distinct clinical entity, affecting up to a third of LC patients; however, its underlying autonomic physiology relative to classic POTS remains poorly defined. We aimed to compare cardiovascular autonomic function, blood volume, and symptom burden between LCPOTS and pre-pandemic POTS.

Hypothesis: We hypothesized that the pathophysiology of LCPOTS is distinct from POTS while sharing underlying causes, namely hypovolemia.

Methods: We performed a secondary analysis of two prospective cohorts at the Vanderbilt Autonomic Dysfunction Center, including 23 patients with classic POTS from 2019–2023 and 21 with LCPOTS from 2023–2026 (age 28.3 ± 7.5 vs. 33.4 ± 9.5 yrs, P=0.077; height 1.68 ± 0.07 vs. 1.67 ± 0.09 m, P=0.625; Weight 67.6 ± 10.5 vs. 69.6 ± 9.7 kg, P=0.536; BMI 24.0 ± 3.3 kg/m2 vs. 25.2 ± 3.4 kg/m2, P=0.298, in POTS vs. LCPOTS respectively). All participants underwent standardized autonomic testing, including heart rate variability (HRV), beat-to-beat blood pressure (BP) monitoring, Valsalva maneuver, and baroreflex sensitivity assessment. Blood volume was measured using a carbon-monoxide rebreathing method. Acute orthostatic symptoms were assessed using the Vanderbilt Orthostatic Symptom Score (VOSS), chronic autonomic symptoms with COMPASS-31, and quality of life using EQ-5D.

Results: Despite similar orthostatic tachycardia and orthostatic symptoms, LCPOTS demonstrated a distinct autonomic profile characterized by higher time-domain HRV (RMSSD: 38.7 vs. 25 ms, p=0.026; pNN10: 39.4% vs. 31.3%, p=0.001) and greater baroreflex sensitivity (LF SBP–RRI gain: 15 vs. 8 ms/mmHg, p=0.003), alongside reduced low-frequency blood pressure variability (1.5 vs. 4.8 $mmHg^2$, p<0.001). Early phase II systolic blood pressure decline during Valsalva was attenuated in LCPOTS (14.6 vs. 22.6 mmHg, p=0.023), indicating improved hemodynamic buffering. Chronic autonomic symptom burden was lower in LCPOTS (COMPASS-31: 35.2 vs. 45.1, p=0.004), although quality-of-life impairments were present in both.

Conclusions: LCPOTS is characterized by enhanced cardiovagal modulation and baroreflex sensitivity with reduced blood pressure variability. These findings suggest that LCPOTS represents a distinct autonomic phenotype, potentially reflecting compensatory autonomic reorganization following viral injury. Recognition of these differences highlights the need for targeted approaches rather than uniform treatment across POTS subtypes.

P.35 - Sex Matters: Differential Effects Of Isoflurane And Surgical Stress On Serum Cholinesterase Activity In Male And Female Wistar Rats

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INTRODUCTION: Volatile anesthetics, such as isoflurane, are used in preclinical and clinical procedures. However, they are not risk-free and have been associated with haemodynamic disturbances, which are attributed partially to autonomic imbalance. Evidence suggests they can affect the cholinergic system, but their role in modulating cholinesterase activity in a sex-specific manner remains unclear. Although biomarkers are still unavailable for clinical use, we have measured serum cholinesterases activity during isoflurane administration as a readout of cholinergic function.

METHODS: Male and female Wistar rats (10-12 weeks) were studied under three distinct protocols (Ethical Approval n°04/2024). Protocol-1 (P1): Combined impact of trauma and anesthesia. Blood was collected before anaesthesia, during femoral artery catheterization under isoflurane (4% induction, 2.5% maintenance), and at 24h/48h post-surgery. Protocol-2 (P2): Isolated anaesthetic effect. Rats were exposed to isoflurane for the same duration as P1 but without invasive intervention. Protocol-3 (P3): Baseline values from animals without anaesthesia or surgery (naïve). Blood obtained from the protocols was processed by sonication and centrifugation. Hemoglobin, acetylcholinesterase activity (AChEa), and butyrylcholinesterase activity (BuChEa) were measured by colorimetric assay and analyzed using one-way ANOVA with post-hoc tests ($p<0.05$).

RESULTS: In P1, males showed no differences between pre- and post-operative stages, but females exhibited increased AChE-a during surgery and decreased BuChE-a after 48h. Across protocols, males showed reduced AChE-a 48h after surgery (P1) vs. naïve rats (P3), with no effect from anaesthesia alone. Conversely, in females, BuChE-a was significantly higher in the anaesthesia-only group (P2) compared to both surgical and control groups.

CONCLUSION: These findings demonstrate that serum cholinesterase activity, linked to autonomic balance, is modulated by isoflurane in a sex-dependent manner. While females show enzymatic sensitivity to the anaesthetic itself, males appear more vulnerable to cumulative surgical stress. This highlights sex as a critical biological variable in perioperative autonomic regulation, suggesting a need for personalised clinical protocols to mitigate cardiovascular risks and optimise recovery differently for men and women. FUNDING: FAPES Grant code: 21/2023 - 749/2024. MSM; LJC; VSM; KBS; BFS; JGMA; TJB: CAPES (Grant Code 01). GGN; BML; PBSA: FAPES. AB: UFES (PIBIC UFES). KNS: CNPq/FAPES 2025-H5S1W fellowship; CNPq/MCTI/FNDCT Nº 44/2024 (402130/2025-1).

P.36 - Autonomically Defined Fear And Recovery States Shape Cortical Activity Patterns

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Autonomic variables are tightly linked to emotional states and can feed back to the brain, in particular to cortical circuits, to shape emotional processing. However, the mapping between autonomic variables and specific adaptive strategies in threatening environments remains poorly understood, as does the way these autonomic patterns influence cortical activity . Canonical defensive responses such as freezing, explosive escape, sustained vigilance to distant threats, and subsequent recovery may each recruit distinct combinations of autonomic and cortical states, but these joint signatures are not well characterized .
To address this issue, we developed a U maze task in which mice received mild footshocks in one arm but could freely escape to a safe arm. Throughout the task, we monitored respiration, heart rate, and body temperature in parallel with local field potentials and single-unit activity in the prefrontal cortex. This approach enabled simultaneous tracking of autonomic and cortical dynamics as animals transitioned between varied fear states states .
In the safe arm, after threat avoidance, we identified a distinct slow-breathing immobility state consistent with post-stress recovery. This state was characterized by 2–4 Hz respiration, reduced heart rate, increased heart rate variability, and reduced peripheral blood flow, and contrasted sharply with classical freezing in the shock arm, which was accompanied by robust autonomic arousal. Post-task stress levels were not predicted by the number of shocks received, but by the balance between time spent in freezing versus the slow-breathing recovery state .
Manipulations targeting network dynamics and pharmacology altered this balance. Disruption of hippocampal sharp-wave ripples reduced the occurrence of the recovery state and increased stress, whereas diazepam promoted this state and reduced stress. At the cortical level, prefrontal activity patterns diverged between freezing and recovery, with subsets of neurons showing distinct firing as a function of fast versus slow breathing. These results indicate that autonomically defined fear and recovery states impose distinct regimes of cortical activity and that stress resilience depends on the balance between defensive and recuperative autonomic–cortical states.

P.37 - Ventilatory Baroreflex In Humans: Is There Evidence Of Hysteresis?

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Introduction: The ventilatory baroreflex is characterized by changes in respiratory activity in response to alterations in arterial blood pressure, with hypotension increasing ventilation and hypertension producing ventilatory inhibition. Although the existence of this reflex has been demonstrated in humans, it remains unknown whether the ventilatory baroreflex exhibits hysteresis, a phenomenon previously described in other baroreflex pathways. Therefore, this study aimed to investigate whether the ventilatory baroreflex displays hysteresis in humans. Methods: Nine healthy adults underwent the modified Oxford technique, involving sequential bolus injections of sodium nitroprusside (65–100µg) followed by 65–100µg phenylephrine hydrochloride 1 min afterwards to induce transient decreases and increases in blood pressure. Beat-by-beat arterial pressure was measured continuously using finger photoplethysmography and ventilation was continuously estimated using a respiratory inductance belt. Changes in mean arterial pressure (MAP) and ventilation (VE) were quantified for each phase, and linear regressions were used to compute slopes of the MAP–VE relationship. Results: Both nitroprusside and phenylephrine produced significant pressor (Δ -16 ± 1 mmHg; $P < 0.001$) and depressor (Δ 22 ± 1 mmHg; $P < 0.001$) responses accompanied by robust ventilatory adjustments (NTP: Δ 5.5 ± 0.8 mV/min; $P < 0.001$; PE: Δ –6.7 ± 1.1 mV/min; $P < 0.001$). However, the slopes of the MAP–VE relationship did not differ between pressure falls and rises (–0.44 ± 0.06 vs. –0.44 ± 0.11 $mV \cdot min^{-1} \cdot mmHg^{-1}$), indicating an absence of directional asymmetry. Conclusion: These findings suggest that the ventilatory baroreflex in healthy humans does not exhibit clear evidence of hysteresis.

P.38 - Voluntary Exercise And The Exerkine Irisin Preserve Blood-brain Barrier Homeostasis Under Chronic Stress

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Background: Chronic restraint stress induces blood-brain barrier (BBB) dysfunction and neuroinflammation, whereas voluntary exercise exerts protective effects. As crucial cellular components of the BBB, pericytes play a vital role in maintaining its structural and functional integrity. However, the exact mechanisms underlying exercise-induced BBB protection, particularly the involvement of circulating factors (exerkines), remain elusive. This study investigated the protective effects of exercise on BBB function and pericyte transcriptomes, followed by an examination of the exerkine irisin as a potential mediator.

Methods: First, Wistar rats were divided into control, chronic restraint stress (ST), and ST with voluntary exercise (ST+EX) groups. We assessed blood pressure, region-specific BBB permeability using an extravascular fluorescent tracer, and transcriptomic alterations in isolated hypothalamic perivascular cells. Next, to determine exerkine involvement, stressed rats were continuously administered irisin or saline via osmotic mini-pumps, after which blood pressure and BBB permeability were evaluated.

Results: Stress elevated blood pressure and significantly increased tracer leakage specifically in the paraventricular nucleus (PVN), indicating region-specific BBB disruption. At the molecular level, RNA sequencing revealed that stress activates TNF-mediated NF-κB and MAPK pathways in perivascular cells, promoting inflammatory remodeling. Voluntary exercise successfully prevented these functional disruptions—restoring blood pressure and PVN permeability—and attenuated the inflammatory transcriptomic changes.
Subsequently, we investigated the specific role of the exerkine irisin. Continuous administration of irisin clearly suppressed both the stress-induced blood pressure elevation and the BBB hyperpermeability in the PVN, mimicking the functional benefits of exercise.

Conclusion: Voluntary exercise preserves BBB homeostasis against stress-induced region-specific dysfunction and perivascular inflammation. The functional benefits observed with irisin administration strongly suggest that this exerkine is a key mediator of the exercise-induced BBB protection. Whether irisin acts directly to modulate the pericyte transcriptome and suppress these inflammatory pathways remains to be elucidated in future studies.

P.39 - Cardiovascular Autonomic Dysfunction After Young Ischemic Stroke

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Introduction: Ischemic stroke frequently causes cardiovascular autonomic dysfunction, which may negatively affect the clinical outcomes. However, most previous studies investigating post-stroke cardiovascular autonomic modulation (CAM) focused on elderly patients, with mean age above 65 years old. To date, no study has exclusively investigated whether young stroke patients (aged 18–55 years) also experience compromised CAM. Therefore, we aimed to assess CAM in young stroke patients.

Methods: In 27 young ischemic stroke patients (mean age 49±5 years old, range 32-54 years, 13 women/14 men) and 24 age- and gender-matched healthy controls (mean 47±6 years old, range also 32-54, age 16 women/8 men), we recorded RR intervals (RRIs), systolic (BPsys) and diastolic blood pressure (BPdia), and respiration at supine rest during the first week after stroke onset. We calculated parameters reflecting total CAM (RRI-standard deviation [RRI-SD], RRI-total powers), predominantly sympathetic CAM (RRI-low-frequency [LF] powers and SBP-LF powers] and parasympathetic CAM (root mean square of successive RRI differences [RMSSD], RRI-high-frequency [HF] powers), sympathetic-parasympathetic balance (RRI-LF/HF ratios), and baroreflex sensitivity (BRS). Values were compared between patients and controls using Student's t-test or Mann-Whitney-U-test. Significance was assumed for $p < 0.05$.

Results: Compared with healthy controls, young ischemic stroke patients showed significantly lower values for RRI, RRI-SD, RMSSD, RRI-HF powers, RRI-LF-powers, RRI-total-powers, and BRS, but higher values of BPdia. Otherwise, bio-signals and autonomic parameters did not differ between the two groups.

Conclusion: Young ischemic stroke patients showed reduced cardiovagal modulation, compromised baroreflex, and increased peripheral sympathetic activity within one first week after stroke onset. These findings are similar as in elderly ischemic stroke patients imply that ischemic stroke may trigger cardiovascular autonomic dysfunction irrespective of the young age.

P.40 - Gut Regulated Associations Of Neuronal Signalling In High Bp (grains-bp): A Randomised Controlled Trial Protocol

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Introduction: Hypertension affects one in three Australian adults and is the leading cause of death globally. Despite the range of available medications, more than half of patients do not have their BP under control due to poor adherence, difficulty finding the right treatment due to side effects, or avoiding medication altogether. Diet plays a crucial role in cardiovascular health, with high-fibre intake shown to lower BP through the production of short-chain fatty acids (SCFAs), formed during fibre fermentation. A clinical trial found that a chemically modified resistant starch that releases SCFAs in the colon (HAMSA/B) significantly reduced BP in hypertensive patients via the gut-brain axis. Although the exact mechanism is still unclear, SCFAs may influence BP .

Aims: To investigate the effects of SCFA supplementation on the gut-brain-immune axis of BP regulation.

Methods: The GRAINS-BP trial will recruit 29 adults with untreated hypertension (≥140/90 mmHg) for a randomised double-blinded, placebo-controlled, cross-over study using the non-commercially available HAMSA/B shakes taken twice daily. Over 48 days including a 20-day washout period, participants will attend four visits at Alfred Hospital, Melbourne. Measurements will include muscle sympathetic nerve activity (MSNA), heart rate variability as an indirect measure of vagal activity using continuous heart rate monitoring, 24-hr ambulatory BP, cognitive and mental wellbeing tests, and gastrointestinal transit time. Faecal, urine, and blood samples will be collected at each visit to assess microbiome, cardiometabolic, renal, and immune markers. Mediation analyses will be performed to determine causation.

Expected Results: The primary outcome of this study is the effect of SCFA supplementation on the autonomic nervous system. Secondary outcomes include changes in 24-hour BP, plasma SCFA levels, immune cell profiles, gut microbiome profiles, cognitive function, quality of life, and gastrointestinal transit time.

Discussion: The GRAiNS-BP trial will help confirm and uncover how SCFA supplementation lowers BP , including whether it acts through the gut–brain axis. By clarifying these mechanisms, the study will strengthen evidence for SCFA supplementation as a viable non-pharmacological treatment for hypertension.

P.41 - Subcellular Mechanism Of Blood Pressure Regulation By Arterial Baroreceptors

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Beat-by-beat blood pressure information is transmitted to the brain for hemodynamic regulation by modulating cardiac contractility, heart rate, and vascular resistance. This information is effectively sensed by arterial baroreceptors. Traditionally, an arterial baroreceptor has been considered a single sensor connected to one myelinated axon—this is known as the one-sensor theory (OST). However, recent electrophysiological and morphological studies suggest that a baroreceptor is not a single sensor, but rather a sensory unit composed of multiple sensor types—supporting the multiple-sensor theory (MST). Within each sensory unit, rapid and slow sensors are responsible for detecting dynamic and static components of blood pressure, respectively, enabling the capture of a complete hemodynamic profile. According to the MST, during vascular stretch, multiple sensors within a unit are activated. At any given moment, the sensor with the highest discharge rate acts as the pacemaker, determining the discharge frequency of the entire unit. Thus, the train of action potentials sent to the brain results from the interactions among these different sensors. In general, rapid sensors fire at high frequencies when the rate of pressure change (dp/dt) surpasses their activation threshold, while slow sensors respond to higher static pressure thresholds and discharge at relatively lower frequencies. Therefore, the pressure trajectory during each heartbeat is accurately represented through the coordinated activity of these mechanosensors. Understanding this coding structure is crucial for comprehending hemodynamic regulation. For decades, under the OST, it was assumed that baroreceptor discharge frequency alone conveyed hemodynamic signals. In contrast, the MST posits that the discharge pattern and frequency, as well as its timing carry essential information. Thus, a deeper understanding of peripheral coding will enhance our knowledge of central nervous system integration and advance the field of neural control of circulation.

TOPIC 02. Autonomic Regulation In Cancer And Tumor–host Interactions

P.42 - Autonomic Skin Responses In Bortezomib Treated Multiple Myeloma

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Introduction: Bortezomib, a proteasome inhibitor and cornerstone in the treatment of multiple myeloma (MM), is associated with the development of neuropathic pain and length-dependent sensory polyneuropathy. The transient receptor potential vanilloid type 1 (TRPV1) channel is expressed on nociceptive C-fibers, where activation promotes calcium influx and neuronal excitability. Beyond pain signaling, TRPV1-positive small sensory fibers contribute to cutaneous vasodilation through neurogenic vascular reflexes, providing a measure of small-fiber function. Experimental studies have identified bortezomib as a potent TRPV1 sensitizer, and treatment-induced neuronal hyperexcitability has been observed during bortezomib exposure. We therefore hypothesize that bortezomib-induced TRPV1 sensitization contributes to pain hypersensitivity and altered cutaneous neurovascular responses in patients receiving bortezomib.

We aimed to investigate whether patients who develop neuropathic pain during bortezomib treatment exhibit increased capsaicin-induced pain and flare responses compared with patients without neuropathic pain.

Methods: A prospective observational cohort study of 40 treatment-naive MM patients initiating bortezomib treatment. At baseline and after 12 weeks, 100 µL of 5% capsaicin was applied to the dorsum of the foot. Pain intensity was assessed every 2 minutes during a 40-minute exposure period using a visual analog scale to estimate AUC. Cutaneous neurovascular responses were assessed using laser speckle contrast imaging (PeriCam PSI System). Flare area was quantified offline using PIMSoft and defined as perfusion values above the baseline mean + 2 SD.

Results: The study is ongoing. Five patients have completed baseline and follow-up assessments. Median capsaicin pain response increased from 0.58 to 0.78. Flare area was stable in four patients, whereas one patient exhibited a marked increase in both flare area and pain response.

Conclusion: Preliminary findings suggest that bortezomib treatment may be associated with changes in capsaicin-evoked pain and cutaneous neurovascular responses in a subset of patients. These observations support further investigation of TRPV1-mediated mechanisms and their potential role in small-fiber dysfunction and neuropathic pain in MM.

TOPIC 03. Sleep, Circadian Rhythms And The Autonomic Nervous System

P.43 - Sleep-twin: Multimodal Sleep Stage Classification In Mice Using A Digital Twin Framework

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Introduction: In biomedical research, digital twin (DT) technology is a game-changer, enabling the creation of virtual physiological representations for intelligent decision-making, predictive modeling, and real-time monitoring. Comprehensive insights into autonomic nervous system activity can be obtained in sleep neuroscience by incorporating brain and cardiovascular information into DT frameworks. This work develops a DT-driven multimodal sleep-monitoring framework for mice that combines machine learning and probabilistic sequence modeling with data from electroencephalography (EEG), electromyography (EMG), heart rate (HR), and blood pressure (BP).

Methods: To capture transitions between wakefulness, non-rapid eye movement (NREMS) sleep, and rapid eye movement (REMS) sleep, we used physiological recordings from 40 mice obtained at the University of Bologna's PRISM laboratory. For all mice, manual scoring of wake–sleep states was performed by 3 trained investigators (S.B., C.B., V.L.M.) on all consecutive 4 s epochs. To enhance data quality and physiological consistency, preprocessing included crucial signal cleaning and normalization. A single dataset representing both electrophysiological and autonomic activity was created by combining multimodal features from EEG, EMG, HR, and BP signals. Initial sleep-stage prediction was performed using a Support Vector Machine (SVM) classifier, temporal sleep-state transitions were modeled, and sequential consistency was enhanced using a Hidden Markov Model (HMM). The physiological sleep states over time were determined by applying the Viterbi decoding algorithm. Results were generated on a High-Performance Computing (HPC) cluster, Galileo100.

Results: SLEEP-Twin achieves a weighted F1 score with an overall accuracy of 95.0%. Wakefulness has an F1 score of 97.23%. This state outperformed the NREM state, which scored 92.48%. Notably, REM sleep categorization achieved an F1 score of 83.35%, demonstrating successful identification of sleep states. Compared with EEG-EMG-only methods, integrating HR and BP signals greatly enhanced REM sleep recognition and reduced misclassification between REMS and NREMS. Sequence stability and physiological continuity during anticipated sleep transitions were improved through temporal refinement using HMM and Viterbi decoding.

Conclusion: SLEEP-Twin provides a precise, physiologically meaningful method for monitoring mice's autonomic and sleep states in real time. Our work integrates multimodal physiological data with probabilistic modeling to enhance preclinical neuroscience, disease analysis, medication monitoring, and sleep healthcare systems.

TOPIC 04. Neuroimmune Communication And Neural Control Of Immune Responses

P.44 - Central Leukotrienes Mediate Lipopolysaccharide-induced Hypothermia

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Introduction: Alterations in body temperature (Tb) are among the earliest responses to infection, manifesting either as an increase (fever) or a decrease (hypothermia). While the central regulation of fever has been extensively studied, particularly the role of prostaglandin E2, an arachidonic acid (AA) metabolite, the mechanisms underlying hypothermia remain poorly understood. Recent evidence indicates that leukotrienes (LTs), another mediator of AA pathway, may contribute to Tb reduction during systemic inflammation. Our objective was to investigate the role of central LTs in the hypothermia induced by lipopolysaccharide (LPS) injection.

Methods: Male Sprague-Dawley rats (300–330 g, housed at 22 °C) were surgically implanted with a lateral ventricle cannula for intracerebroventricular (icv) injections, a jugular vein catheter for intravenous (iv) administration, and an abdominal datalogger for Tb monitoring. After recovery from the surgeries, animals received an icv administration of MK-886 (an inhibitor of LT synthesis, 4mg/kg), montelukast (LTC4 receptor antagonist, 200ng), SC-236 (COX-2 inhibitor, 150ng) or vehicle (DMSO) thirty minutes before iv injection of LPS in a dose that induces hypothermia (1.5 mg/kg) or saline as control. Tb was monitored for 6 hours and thermographic images were obtained using an infrared camera.

Results: LPS induced marked hypothermia, which was significantly attenuated by MK-886 (-1.19±0.04°C DMSO vs. -0.2±0.05°C MK-886, 90 min after injection). No difference was observed in saline-injected animals (0.09±0.03°C DMSO vs. 0.24±0.06°C MK-886). Thermographic data demonstrated that blocking LT synthesis reduces heat loss during the hypothermic phase (HLI=0.37±0.12 DMSO vs. 0.22±0.09 MK-886). Central administration of montelukast attenuated LPS-induced hypothermia, but to a lesser degree than MK-886 (-0.46±0.3°C), while SC-236 does not alter the hypothermic profile (-1.29±0.2°C).

Conclusion: Our results indicate that central synthesis of leukotrienes is an important mechanism involved in the Tb reduction observed during an immune stimulus with LPS.

P.45 - Splenic Denervation Improves Arterial Pressure And Autonomic Dysfunction In Renovascular Hypertension

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Introduction: Growing evidence indicates that splenic innervation and neuroimmune activation play key roles in the development of systemic arterial hypertension (SAH). This study investigated the effects of splenic denervation on blood pressure, sympathetic activity, and microglial cell count in a rat model of 2K1C renovascular hypertension.

Methods: Male Wistar rats underwent either splenic or left renal denervation, followed by extrinsic constriction of the left renal artery to induce renovascular hypertension. Left renal denervation was included as a comparative intervention because of its well-established antihypertensive effects. Six weeks later, cardiovascular and autonomic parameters, as well as baroreflex sensitivity, were evaluated. Blood, spleen, and brain samples were collected for histological and molecular analyses.

Results: Hypertensive rats (2K1C) exhibited elevated mean arterial pressure (MAP) (189.2 ± 13.5 mmHg), increased baseline renal (rSNA: 173.1 ± 18.1 spikes/sec) and splenic (sSNA: 160.3 ± 32.9 spikes/sec) sympathetic nerve activity, and impaired baroreflex sensitivity ($\alpha = 0.29 \pm 0.03$; $\alpha' = -0.74 \pm 0.20$). Splenic denervation (2K1C+sDN) significantly reduced MAP (134.2 ± 30.3 mmHg) and attenuated sympathoexcitation (rSNA: 122.6 ± 32.4 spikes/sec), producing effects comparable to those observed after renal denervation. In addition, 2K1C rats displayed splenic white pulp hypertrophy, increased mobilization of lymphocytes and monocytes into the circulation, and a higher microglial cell count in the RVLM compared with normotensive controls. Notably, splenic denervation ameliorated these alterations to a similar extent as renal denervation (2K1C+rDN).

Conclusions: Renovascular hypertension is characterized by both systemic and neuroinflammation, which contribute to cardiovascular and autonomic dysfunction. Our findings suggest that heightened splenic nerve activity promotes inflammatory responses and autonomic impairment, thereby contributing to both the development and maintenance of renovascular hypertension.

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P.46 - Systemic And Cutaneous Immune Signatures In Autoimmune-associated Idiopathic Small Fiber Neuropathy

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Small Fiber Neuropathy (SFN) is a peripheral nervous system disorder characterized by neuropathic pain, sensory disturbances, and autonomic dysfunction. Up to 50% of cases remain idiopathic (iSFN), with increasing evidence suggesting an autoimmune aetiology in a subset of patients. Our previous work identified novel candidate autoantibody targets in SFN, supporting a potential immune-mediated disease mechanism. We hypothesized that autoimmune SFN (aSFN) is associated with both systemic immune dysregulation and local immune activity within affected tissue.

Peripheral blood mononuclear cells (PBMCs) from two aSFN patients with autonomic disturbances and hypocomplementemia, and two age-matched healthy controls, underwent single-cell RNA sequencing. Calf skin biopsy sections were stained with CD45, CD68, CD31, IgG, macrophage migration inhibitory factor (MIF), and myxovirus resistance protein 1 (MX1). MIF and MX1 were selected based on previous identification as candidate autoantibody targets in aSFN. Sections were analysed using confocal microscopy.

Single-cell RNA sequencing demonstrated increased proportions of γδ T cells, class-switched memory B cells, activated B cells, early plasmablast-like B cells, and CD8+ mucosal-associated invariant T (MAIT) cells in aSFN patients compared with healthy controls. Transcriptional analysis revealed enhanced stress-response and T-cell receptor signalling pathways in γδ T cells and MAIT cells, together with increased cytotoxic signatures in effector natural killer cells.

Skin immunofluorescence identified multiple immune-rich microenvironments within patient skin that were largely absent in healthy controls. These microenvironments exhibited heterogeneous compositions and distributions between patients and were characterised by recurring patterns of IgG deposition, antigen-associated signals, and immune-cell infiltration. Notable features included overlapping IgG and antigen-associated signals across multiple z-planes and on vessel-like structures corresponding to CD31-positive structures. Using anatomical landmarks, regions containing IgG+, antigen-associated and DAPI+ signals frequently aligned with CD45+ antigen-associated cells and, to a lesser extent, CD68+ antigen-associated cells on consecutive sections. Overall immune-cell abundance and localisation to these microenvironments were increased relative to healthy controls.

These findings demonstrate evidence of both systemic and local immune dysregulation in aSFN. The combination of expanded immune-cell populations in peripheral blood and immune-rich cutaneous microenvironments containing IgG deposition, antigen-associated signals, and infiltrating immune cells supports an immune-mediated disease mechanism.

TOPIC 05. Vagus Nerve Modulation And Bioelectronic Therapeutic Approaches

P.47 - Thermal Effects Of Kilohertz-frequency Nerve Block In The Vagus Nerve Of Rats

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Introduction: Although vagus nerve stimulation (VNS) has great potential for the treatment of autonomic dysfunction, involuntary laryngeal muscle contraction during the stimulation is still a problematic side effect that limits therapeutic potential. Kilohertz-frequency (KHF) nerve block as an adjunct to VNS can overcome this limitation by blocking Aα-fibers to eliminate off-target muscle contraction. However, the much higher duty cycle of KHF stimulation relative to standard VNS requires greater energy delivery that may cause unintended heating and consequent changes in neural activity. Crucially, the thermal effects of KHF stimulation during nerve block have not been examined.

Methods: In isoflurane-anesthetized rats, we used cuff electrodes to activate (3.096 Hz) and block (10 or 20 kHz) myelinated and unmyelinated fibers of the cervical vagus nerve (N = 6, 5 females). We measured the temperature inside the block electrode using a thermocouple and quantified the neural activity with compound action potentials. In a subset of trials, we introduced additional resistive heating by superposing the blocking signal with a much higher frequency signal (40 or 80 kHz) at amplitudes that heated the tissue but did not, on their own, produce nerve block.

Results: The temperature in the electrode increased by 0.08 °C (10 kHz) [CI: 0.02-0.13] and 0.14 °C (20 kHz) [CI: 0.09-0.19] when blocking 50% of myelinated fibers; by 0.7 °C (10 kHz) [CI: 0.55-0.84] and 1.77 °C (20 kHz) [CI: 1.59-1.95] when blocking 50% of unmyelinated fibers. In the subset of trials where we superposed resistive heating of >1 °C, the heating increased the degree of block (N = 2) and caused post-stimulation block to persist for longer (1 s) in unmyelinated fibers (N = 1).

Conclusion: KHF increases temperature measurably within the parameters used for nerve block, and blocking unmyelinated fibers results in a 10-fold increase in temperature over blocking myelinated fibers. We will further investigate the thermal effect on nerve block in view of ion channel kinetics and ion concentration, which have been hypothesized to correlate with the post-stimulation block as well.

P.48 - Electrical Vagal Stimulation Regulates Peripheral Orexin Levels In Experimental Endotoxemia

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Backround: The cholinergic anti-inflammatory pathway is a neuroimmune mechanism mediated through the vagus nerve and α7 nicotinic acetylcholine receptors (α7nAChR). Orexin neurons regulate autonomic function at multiple levels of the central autonomic network, from limbic structures to premotor autonomic centers and sympathetic preganglionic neurons. This study aimed to investigate the effects of electrical vagal stimulation (VS) on orexin production in visceral organs during endotoxemia and to evaluate the relationship between tissue orexin levels and α7nAChR expression.

Methods: Adult Wistar albino rats (200–250 g) of both sexes received vehicle or the dual orexin receptor antagonist almorexant (ALM; 30 mg/kg, i.p.) for 3 days. On day 4, endotoxemia was induced by lipopolysaccharide (LPS, Escherichia coli serotype O111:B4; 10 mg/kg, i.p.). Half of the LPS-treated animals underwent cervical vagal stimulation for 20 min. Six hours after LPS administration, animals were sacrificed, and stomach, small intestine, colon, liver, and kidney tissues were collected. Orexin-A and orexin-B levels were determined by ELISA, while α7nAChR mRNA expression was quantified by real-time PCR. Statistical analyses were performed using one-way ANOVA followed by appropriate post hoc tests. Pearson correlation and simple linear regression analyses were used to examine the relationship between tissue orexin levels and α7nAChR expression. Statistical significance was accepted as $p<0.05$.

Results: Endotoxemia significantly increased orexin-A and orexin-B levels in nearly all examined tissues, whereas VS markedly reduced these elevations. LPS decreased α7nAChR mRNA expression, while VS significantly restored receptor expression. Pretreatment with ALM abolished the beneficial effects of VS on α7nAChR expression, suggesting the involvement of orexin signaling in vagal modulation of the cholinergic anti-inflammatory pathway. Blockade of orexin receptors prevented beneficial effects of VS on α7nAChR expression. Correlation and regression analyses demonstrated a significant positive association between tissue orexin-A levels and α7nAChR mRNA expression.

Conclusions: Electrical vagal stimulation modulates peripheral orexin signaling and restores α7nAChR expression during endotoxemia. Orexin signaling contributes to activation of the cholinergic anti-inflammatory pathway. These findings suggest a functional interaction between orexin and α7nAChR signaling in the regulation of peripheral inflammation and identify the orexin system as a potential therapeutic target for inflammatory disorders.

P.49 - The Adaptive Immune System Response Mediates The Loss Of Long-term Muscle Opsin Expression In Channelrhodopsin-based Optogenetics

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Introduction: ChR2-based optogenetics expressed in skeletal muscle wanes over time. Previously, we show that targeted immunosuppression with a combination of rapamycin and cyclosporin prevents loss of transgene expression, and after 12 weeks we found sustained, robust transgene expression and functional efficacy of the optogenetic control of muscles. This identifies the host adaptive immune response as the critical factor for the long-term transgene expression in muscle. The current study examines the mechanisms by which the host adaptive immune system targets the muscle transduced by an AAV9-tMCK-ChR2:mCherry vector.

Methods: Female and male Sprague-Dawley (SD) rats (N=24; 12M:12F) were assigned into three treatment groups of 8 SD rats (4 male, 4 female) to receive via intraperitoneal (i.p.) delivery of an immunosuppression regimen or control: 1. Prednisolone, 2. Rapamycin and Cyclosporin, 3. Vehicle controls. After 1 week, all rats received an identical intramuscular injection of the AAV9-tMCK-ChR2:mCherry, and drug treatments maintained weekly for 12 weeks. Tongue transgene and protein expression were evaluated using RNA and DNA PCR. Anti-AAV antibody concentration was determined using ELISA and combined fluorescence immunohistochemistry and Masson's trichrome staining to determine the infiltration of immune cells into tongue and tissue fibrosis.

Results: Transgene mRNA expression and opsin DNA levels were significantly elevated in the tongues of animals treated with rapamycin/cyclosporin compared to vehicle and prednisolone-treated cohorts. Low levels of transgene mRNA and DNA were detected in the heart, liver, and spleen across cohorts, with no significant intergroup differences ($p > 0.05$). Anti-AAV antibodies were detected in vehicle- and prednisolone-treated animals, with titres increasing up to 12 weeks post-treatment; no antibodies were detected in the rapamycin/cyclosporin cohort. $CD8^+$ cell infiltration was present in the tongues of vehicle- and prednisolone-treated animals but absent in the rapamycin/cyclosporin group. $Foxp3^+$ cells were observed at low levels across all cohorts, while $CD19^+$ cells were not detected in any group. Histological assessment revealed increased tissue fibrosis in vehicle- and prednisolone-treated tongues, evidenced by elevated collagen deposition.

Conclusion: AAV-delivered opsins lack long-term functional expression due to the immunogenic component of the AAV. Future optogenetic muscle stimulation treatments may require the use of alternate opsins and/or opsin delivery methods.

P.50 - Optogenetic Vagus Nerve Stimulation: A Novel Strategy To Prevent Respiratory Dysfunction, Neurodegeneration, And Astrocytosis In The 6-hidroxydopamine Model Of Parkinson's Disease.

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Neuroinflammation plays a critical role in neuronal death within Parkinson's Disease (PD). In the 6-hydroxydopamine (6-OHDA) model of PD, glial-mediated neuroinflammation drives the degeneration of key respiratory nuclei, such as the preBötzinger complex (preBötC) and the retrotrapezoid nucleus (RTN), consequently leading to respiratory deficits. Vagus nerve stimulation (VNS), known to mitigate pro-inflammatory cytokine production via the cholinergic anti-inflammatory reflex, emerges as a potential strategy for PD prevention. To investigate the effects of stimulating the afferent and efferent portions of the vagus nerve (X) in the 6-OHDA model, VGLUT-cre:Ai32 or Chat-cre:Ai32 mice (CEUA nº 4061131021) underwent stereotaxic surgery for striatal injection of 6-OHDA (10 µg/µl) or vehicle. Five days post-surgery, the left X was isolated and stimulated with blue light (5Hz, 10 min). Another five days later, diaphragmatic activity was recorded via electromyography, followed by perfusion and immunohistochemical analysis of the brain. Diaphragmatic activity analysis revealed that the 18.4% (VGLUT-cre:Ai32) and 28.6% (Chat-cre:Ai32) reduction in diaphragm firing frequency in the 6-OHDA group was prevented in mice receiving stimulation of the afferent ($p=0.01$) and efferent ($p=0.01$) portions of X, respectively. No significant differences were observed in inspiratory time (VGLUT-cre:Ai32 $p=0.31$,Chat-cre:Ai32 $p=0.23$), or expiratory time (VGLUT-cre:Ai32 $p=0.56$, Chat-cre:Ai32 $p=0.85$). Although X stimulation did not prevent the 81% loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta ($p<0.0001$), both afferent and efferent stimulation of X nerve prevented astrocytosis in this region ($p=0.02$), prevented the 27.14% loss in the NK1R+ preBötC neurons ($p=0.01$) and the 71.7% loss in the PHOX2B+ neurons in the RTN ($p=0.02$). Furthermore, afferent stimulation was capable of reducing astrocytic density in the preBötC ($p=0.03$), while efferent stimulation reduced this density in the RTN ($p=0.02$). These results highlight the potential of VNS as a strategy for alleviating respiratory deficits in this PD model.

TOPIC 06. Autonomic Dysfunction In Neurodegenerative And Orthostatic Disorders

P51 - Alteration Of Heart Rate Variability Response To Co2 In Different Epileptic Rat Models

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Sudden Unexpected Death in Epilepsy (SUDEP) remains a major concern, particularly in patients with generalized tonic-clonic seizures. Increasing evidence suggests that autonomic dysfunction, including central apnea and cardioventilatory failure, plays a key role in its pathophysiology. Central chemoreception, which mediates respiratory responses to elevated brain CO_2 levels, has been shown to be impaired in chronically epileptic rats alongside altered heart rate variability (HRV). This study investigates HRV responses to hypercapnic challenge in two epileptic rat models to identify potential autonomic deficits associated with SUDEP.
Wistar and Sprague-Dawley rats injected with kainic acid (KA) to induce temporal lobe epilepsy (TLE), as well as Genetic Absence Epilepsy Rats from Strasbourg (GAERS), were compared with their respective controls (healthy Wistar, Sprague-Dawley, and non-epileptic rats). HRV was assessed by photoplethysmography during a 3-hour protocol consisting of 1 hour of baseline normocapnia, 1 hour of hypercapnia (10% CO_2), and 1 hour of recovery under normocapnia. HRV metrics (SDNN, RMSSD, LF, HF, and LF/HF ratio) were analyzed at six 5-minute time points throughout the protocol.
Preliminary results showed that control groups exhibited a marked increase in HRV metrics during early hypercapnia and recovery, returning to baseline within 40 minutes. In contrast, epileptic rats displayed a blunted HRV response to CO_2 and delayed recovery to baseline, with GAERS showing relatively preserved responses compared with TLE models (KA Wistar/Sprague-Dawley). These findings suggest that epilepsy impairs autonomic reactivity to hypercapnia, while seizure type further modulates this effect. Differences between epileptic models appeared minimal, highlighting epilepsy itself as the primary driver of autonomic dysfunction.
This work provides new insights into SUDEP risk factors by emphasizing the contribution of autonomic dysregulation in epilepsy. Further studies are needed to validate these findings and explore therapeutic strategies targeting chemoreception pathways to reduce SUDEP risk.

P.52 - Exercise-induced Respiratory Variability Is Associated With Motor Severity In Moderate Parkinson's Disease

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Introduction: Respiratory dysfunction is a well-recognized feature of Parkinson's disease (PD), even in mild to moderate stages, including altered breathing patterns, reduced respiratory muscle strength, and impaired ventilatory responses. These abnormalities reflect dysfunction across central respiratory networks, chemosensory pathways, and motor activation of respiratory muscles. Because breathing depends on integration between neural drive and motor output, motor impairment in PD may be reflected not only in locomotor performance but also in the stability of respiratory control. Motor symptom severity (MDS-UPDRS Part III) may serve as a proxy of neurophysiological dysfunction affecting both locomotor and respiratory systems. However, the relationship between respiratory control and motor severity remains poorly understood. We examined whether respiratory variability during maximal exercise, a dynamic measure of ventilatory control under physiological stress, is associated with motor symptom severity in PD. Methods: Twenty-four individuals with idiopathic PD (15 men; 66 ± 8 years) performed a maximal cardiopulmonary exercise test using individualized ramp protocols. Breath-by-breath respiratory variables were measured via indirect calorimetry, including minute ventilation (V̇E), respiratory frequency (fR), and tidal volume (VT). Time-domain indices of respiratory variability [standard deviation (SD) and root mean square of successive differences (RMSSD)] were calculated and normalized by the number of breaths (SD/n and RMSSD/n). Motor symptom severity was assessed using the MDS-UPDRS Part III. Correlation and partial correlation analyses (controlling for age, sex, and BMI) were performed. Results: No significant associations were observed between respiratory variability and motor severity in the full cohort (all $p>0.52$). Stratified analysis revealed no associations in patients with mild motor impairment (MDS-UPDRS ≤32; all $p>0.15$). In contrast, in patients with moderate motor impairment (n=14; MDS-UPDRS 33–58), higher motor severity was positively correlated with RMSSD/n of V̇E ($r=0.697$, $p=0.006$) and fR ($r=0.698$, $p=0.006$). These relationships remained significant after adjustment for covariates (V̇E: $r=0.84$, $p=0.001$; fR: $r=0.77$, $p=0.005$). No significant associations were found for VT or SD-based indices. Conclusion: In moderate PD, greater motor symptom severity is associated with increased short-term respiratory variability during exercise. These findings suggest that respiratory variability during progressive maximal exercise may represent a sensitive and informative marker of disease-related physiological dysfunction in PD.

P.53 - Characterization Of Autonomic Dysfunction In Prodromal And Early Stages Of Parkinson's Disease

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Objective: To evaluate cardiovascular autonomic dysfunction across prodromal stages of synucleinopathies (Pure Autonomic Failure-PAF); isolated REM Sleep Behavior Disorder-iRBD) and early stages of Parkinson's disease (PD), assessing both sympathetic and parasympathetic functions.

Background: Autonomic dysfunction is considered a prodromal marker of synucleinopathies, often manifesting years before the onset of motor symptoms. However, no studies have comprehensively evaluated or compared cardiovascular dysfunction profiles in PAF, iRBD, and earlyPD.

Methods: Cardiovascular autonomic functions were assessed in PAF patients from the "IAF-BO cohort"; iRBD patients from the "iRBD cohort" and earlyPD patients from the "BoProPark study". Cardiovascular reflex tests (CRTs) were performed at the time of first diagnosis and included the head-up tilt test (HUTT), Valsalva manoeuvre (VM), deep breathing (DB), cold face (CF) and handgrip (HG) under continuous blood pressure (BP) and heart rate (HR) monitoring. Group comparisons were made using Kruskal-Wallis and chi-square tests.

Results: The study included 72 PAF patients (age: 64.00[14.00] years, disease duration: 6.00[5.50] years); 67 iRBD (age: 68.0[8.00] years, disease duration:4,50[6,50] years) and 99 PD (age: 63,50[11.50] years, disease duration: 1,50[1,00]years).

Cardiovascular autonomic dysfunction was detected in 100% of PAF patients, 37% of iRBD patients and 9% of PD patients. PAF patients showed a significantly higher BP drop at HUTT and reduced BP responses during VM (overshoot, SBP IIb-IIa) compared to iRBD and PD. Additonally, iRBD patients exhibited significantly reduced BP responses at HUTT and VM compared to PD.

PAF patients also presented pathological Valsalva ratio (VR) and inspiration/expiration HR ratio (I/E) compared to both iRBD and PD. Furthermore, iRBD patients showed lower VR and I/E compared to PD. Responses to CF and HG were reduce exclusively in PAF patients.

Conclusion: Cardiovascular autonomic dysfunction is already severe in PAF patients at the first evaluation, affecting both sympathetic and parasympathetic functions. In iRBD patients, early impairment of sympathetic baroreflex function is detectable, with milder involvement observed in PD patients. This study highlights the distinct autonomic profiles of PAF, iRBD, and PD, suggesting that prodromal stages do not fully represent the entire PD population.

P.54 - Orthostatic Intolerance And Cardiovascular Autonomic Control: Should We Phenotype The Patients?

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Introduction. Orthostatic intolerance (OI) is characterized by symptoms occurring in the upright posture and relieved by recumbency, including lightheadedness, weakness, nausea, brain fog, and exercise intolerance. In younger individuals, OI is frequently associated with postural orthostatic tachycardia syndrome (POTS). However, many patients with pronounced OI symptoms do not fulfill POTS diagnostic criteria despite significant impairment in daily functioning. This study investigated cardiovascular autonomic regulation in young patients with OI and sought to identify potential subclinical autonomic abnormalities.

Methods. Between January 2023 and December 2025, 38 consecutive patients aged ≤50 years with relevant OI symptoms were evaluated at the Autonomic Disorders Clinic of Policlinico Hospital, Milan. All underwent standardized head-up tilt testing (HUTT): 10 minutes of supine rest followed by a 70° head-up tilt for 15 minutes. Fifteen patients fulfilled POTS diagnostic criteria (heart rate increase >30 bpm; OI-HUTTpos), whereas 23 showed no significant heart rate or blood pressure abnormalities (OI-HUTTneg). Continuous ECG recordings were obtained, and heart rate variability (HRV) was assessed using nonlinear symbolic analysis. Fifteen age- and sex-matched healthy controls (CTR) underwent the same protocol.

Results. OI-HUTTpos patients exhibited higher heart rates than CTR during supine rest and than both CTR and OI-HUTTneg patients during orthostatic position (CTR: 84±11 bpm; OI-HUTTneg: 89±8 bpm; OI-HUTTpos: 107±11 bpm; $p<0.001$). Symbolic analysis revealed increased sympathetic and reduced parasympathetic modulation during orthostasis of OI-HUTTpos patients compared with both controls and OI-HUTTneg patients, as indicated by higher 0V% values (CTR:40.6±8.7%; OI-HUTTneg:41.8±9.7%; OI-HUTTpos:52.6±11.6%; $p=0.002$) and lower 2LV% values (CTR:7.1±3.4%; OI-HUTTneg:6.2±3.1%; OI-HUTTpos:3.8±2.2%; $p=0.01$), respectively. Conversely, autonomic indices did not differ between OI-HUTTneg patients and healthy controls.

Conclusions. Young patients with pronounced OI and POTS demonstrated altered cardiovascular autonomic regulation during orthostatic stress, whereas OI patients without HUTT abnormalities showed autonomic profiles comparable to healthy controls. Despite reporting symptoms similar to those of patients with confirmed POTS, this latter cohort may represent either a population with altered interoceptive processing mechanisms, still poorly understood from a physiological perspective, or an early stage of cardiovascular autonomic dysfunction preceding overt dysautonomia. Lastly, HRV-based phenotyping may help refine the clinical characterization of OI patients and guide therapeutic management.

Avenue media
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P.55 - Underrecognized Small Fiber Neuropathy And Autonomic Dysfunction In Patients With Spondyloarthritis

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Introduction: Spondyloarthritis (SpA) causes chronic musculoskeletal pain, but its relationship with peripheral autonomic and sensory small-fiber damage is poorly understood. Small fiber neuropathy (SFN) selectively involves thinly myelinated $A\delta$ and unmyelinated C fibers, which mediate both nociception and autonomic function. We investigated the prevalence and characteristics of objective dysautonomia and small-fiber impairment in a cohort of SpA patients.

Methods:We retrospectively analyzed eight adult patients with concomitant SpA and SFN. SFN and autonomic involvement were characterized using clinical phenotypes alongside objective structural and functional testing. This included skin biopsy for distal intraepidermal nerve fiber density (IENFD) and formal autonomic function testing—primarily quantitative sudomotor axon reflex testing (QSART) and tilt-table testing (TTT). Large-fiber polyneuropathy was excluded via normal routine nerve conduction studies (NCS).

Results: All eight patients were female (median age 37.5 years). While burning pain and paresthesia were common, autonomic symptoms were highly prominent features of the presentation. Patients frequently reported cardiovascular dysautonomia (orthostatic intolerance and palpitations), sudomotor dysfunction (impaired sweating or hypohidrosis), and gastrointestinal symptoms. Objective autonomic testing demonstrated sudomotor and/or cardiovagal dysfunction in 6 of 8 patients, revealing marked upper/lower limb sweat volume reductions on QSART and positive orthostatic intolerance on TTT. Structurally, 5 of 8 patients showed reduced distal IENFD on skin biopsy. Autonomic and sensory phenotypes often developed after SpA onset and persisted independently of, or disproportionate to, musculoskeletal inflammatory activity. Standard etiological screening found no superior alternative causes for dysautonomia.

Conclusion: Concomitant SFN and autonomic failure are underrecognized contributors to the global symptom burden in SpA. Overlooking these autonomic features may lead to unnecessary escalation of anti-inflammatory therapy rather than targeted dysautonomia management. Autonomic testing should be considered in SpA patients with unexplained orthostatic or sudomotor complaints.

P.56 - Heartbeat-evoked Potentials And Symptom Recognition In Patients With Orthostatic Hypotension During Tilt-table Testing

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Introduction: Symptoms of classical orthostatic hypotension (cOH) are not fully explained by the magnitude of the orthostatic blood-pressure reduction. Altered interoceptive processing may contribute to reduced symptom awareness in some patients. Heartbeat-evoked potentials (HEPs), electrophysiological markers of cardiac interoceptive processing, have been reported to vary with blood pressure, heart rate, and stroke volume in healthy controls. We investigated whether HEPs differed between patients with cOH and controls during tilt-table testing (TTT), whether these differences depended on haemodynamic changes, and whether HEPs varied with symptom reporting among patients.

Methods: We retrospectively reviewed our TTT database for patients with a clinical presentation and haemodynamic response compatible with cOH, and for controls without cOH or other TTT abnormalities. TTT included concomitant blood-pressure, electrocardiographic, and electroencephalographic monitoring. HEP amplitude was quantified at Cz during supine and upright in early (100–250ms) and late (250–500ms) post-R-wave windows. Linear mixed-effects models included position, group, and their interaction, with a participant-specific random intercept and position-specific residual variances. Secondary models added haemodynamic and electrocardiographic variables as time-varying covariates.

Results: We included 149 participants: 81 controls and 68 patients. Sex distribution did not differ between groups (p=.874), although patients were older than controls (mean age 67.37 vs 64.25 years; p=.033). Early HEP amplitude showed no evidence of position, group, or position-by-group effects. Late HEP amplitude differed between supine and upright conditions (F[1,149]=4.15, p=.044), with a non-significant trend for a position-by-group interaction (F[1,149]=3.66, p=.058). Among patients, late HEP decreased from supine to upright by 2.92μV (95% CI 0.75–5.08; p=.009), whereas no positional difference was observed in controls (p=.928). Higher stroke volume was associated with higher late HEP amplitude (B=0.046; F[1,174.98]=4.48, p=.036). After adjustment for stroke volume, there was no evidence of position (p=.503), group (p=.244), or interaction effects (p=.098).

Conclusion: Standing upright was associated with altered late HEP amplitude, suggesting position-dependent modulation of cardiac interoceptive processing. The association between stroke volume and late HEP, together with the differential positional response in cOH cases and controls, suggests that haemodynamic changes may contribute to interoceptive variation during orthostatic challenge. Further analyses will examine whether symptom recognition is associated with HEP dynamics.

Avenue media
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P.57 - Physical Exercise Prevents Cardiorespiratory Nuclei Degeneration, Breathing And Baroreflex Dysfunction In 6-ohda Parkinson's Disease Rat Model

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INTRODUCTION: Parkinson's disease (PD) is a neurodegenerative disease marked by the progressive loss of dopaminergic neurons in the Substantia Nigra (SN). In addition to its hallmark motor symptoms, PD also presents cardiorespiratory deficits. In the 6-hydroxydopamine (6-OHDA) PD animal model, neurodegeneration extends to cardiorespiratory regions, leading to significant impairments in cardiorespiratory function.
AIM: This study aimed to evaluate whether physical exercise (EX) can prevent neurodegeneration in cardiorespiratory nuclei and mitigate cardiorespiratory deficits in 6-OHDA animals.

METHODS: Male adult rats received intrastriatal injections of either 6-OHDA (24ug/ul) or vehicle (CEUA: 1342290421). EX was initiated 12 days after PD induction and continued for 28 days. On the 40th day, animals underwent whole-body plethysmography, vein and arterial cannulation, baroreflex sensitivity assessments (mean arterial pressure – MAP, and heart rate - HR), perfusion, and brain dissection.

RESULTS: 6-OHDA administration significantly reduced the number of TH+ neurons in the SN, and EX failed to reverse this effect, confirming the PD model ($p<0,0001$). At normoxia, 6-OHDA animals showed a reduced respiratory frequency (fR), which was prevented by EX ($p<0,0001$). This protective effect of EX was also observed under hypercapnia ($p=0,0062$). Additionally, EX prevented the reduction of phox2b-expressing neurons in cNTS ($p<0,0001$), iNTS ($p<0,0001$), and RTN ($p=0,0003$), as well as the loss of NK1R-expressing neurons in rVRG and preBotC, and in ChAT+ neurons in NA ($p<0,0001$). Baroreflex sensitivity was impaired in the sedentary 6-OHDA animals, but EX preserved this function (Phenylephrine – MAP: $p<0,0001$; HR: $p<0,0001$; Sodium nitroprusside – MAP: $p<0,0001$; HR: $p<0,0001$). Correlation between variables after clustering showed that 6-OHDA+EX animals tend to be closer to vehicle animals, which implies a recovery of function of these animals to a baseline condition.

CONCLUSION: EX effectively prevented cardiorespiratory impairments and neurodegeneration in the 6-OHDA PD model, highlighting its potential as a non-pharmacological intervention for preserving autonomic and respiratory function. FINANCIAL SUPPORT: FAPESP 2023/0098-7

P.58 - Lower Urinary Tract Symptoms In Parkinson's Disease: Prevalence And Etiology

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Introduction: Lower urinary tract symptoms (LUTS) are common autonomic manifestations of Parkinson's disease (PD), frequently preceding or accompanying motor progression and significantly impairing quality of life. However, the relationship between LUTS, motor severity, and disease characteristics remains incompletely defined. The aim of this study was to assess the prevalence and pattern of LUTS in PD and to explore their associations with motor severity, disease duration, and quality of life.

Methods: We conducted a cross-sectional observational study including 153 patients with idiopathic PD (mean age 67.4 ± 8.9 years, disease duration 6.1 ± 4.2 years, 58% male). LUTS were evaluated using the Overactive Bladder Questionnaire short form (OAB-qSF) and the International Prostate Symptom Score (IPSS). Quality of life was assessed using disease-specific patient-reported measures. Correlation and multivariate linear regression analysis were performed.

Results: Overall 107 patients (69.93%) reported at least one LUTS. Storage symptoms predominanted (66.35%) with nocturia (61.68%) and urgency (48.59%) being most frequent. Mean OAB-q symptoms score was 38.7 ± 17.4, and mean IPSS total score was 12.4 ± 6.3. OAB-q scores correlated significantly with UPDRS-III ($r = 0.35$, $p < 0.001$), H&Y stage ($r = 0.33$, $p < 0.001$), age ($r = 0.21$, $p=0.001$), and disease duration. In multivariate analysis, UPDRS-III and age independently predicted LUTS severity. Higher LUTS burden was independently associated with poorer quality of life ($p < 0.001$).

Conclusion: LUTS are highly prevalent in PD, with storage symptoms predominating, and are strongly associated with motor severity and disease progression.

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P.59 - Orthostatic Hypotension In Patients With Neurodegenerative Synucleinopathies: Real-world Clinical And Therapeutic Outcomes From An Italian Cohort

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Background: Neurogenic orthostatic hypotension (nOH) could be a characteristic feature of patients with neurodegenerative disorders. Due to the frequency of nOH in some neurological populations, clinicians need to be well informed about its diagnosis and management.

Methods: We selected three cohorts as models of nOH associated with neurological diseases: patients with nOH due to pure autonomic failure (PAF), multiple system atrophy (MSA), or dementia with Lewy bodies (DLB). We retrospectively evaluated 67 patients referred to the Autonomic Laboratory of the IRCCS Istituto delle Scienze Neurologiche of Bologna. Demographic, clinical, and therapeutic data were collected, including treatment outcomes up to the last available follow-up.

Results: Among these patients, 43 were diagnosed with PAF, 12 with MSA and 12 with DLB; the mean follow-up duration was 8 (± 2) years. Overall, 52 patients (77%) were men and 15 (22%) were women. The mean age at disease onset was 71 ± 11 years. Orthostatic hypotension was present at disease onset in all three cohorts and was associated with additional autonomic symptoms. Of these, erectile dysfunction was the most common autonomic manifestation among men, affecting 35 patients (52%), whereas sweating abnormalities and genitourinary dysfunction were the most frequent autonomic symptoms among women, affecting 15 patients (22%). At the last follow-up, 39 patients (58%) were receiving treatment with droxidopa (DOPS) at a median daily dose of 800 [IQR 600-1600] mg, either as monotherapy or in combination with fludrocortisone in 15 patients (22%), midodrine in 15 patients (22%), or both agents in 30 patients (45%). Symptomatic improvement, reflected by better orthostatic tolerance and a reduction in syncopal episodes, was observed in 49 patients (73%). Treatment was discontinued because of lack of efficacy in four cases, while adverse effects were reported in four patients; only one patient experienced a major adverse event. No treatment-related deaths were observed among the eleven patients who died during follow-up.

Conclusions: nOH is a common and under-recognized symptom in neurological diseases. Real-world data regarding treatment with drugs acting on blood pressure showed encouraging results. To our knowledge, this represents the first Italian cohort providing detailed therapeutic outcomes in these conditions.

P.60 - Diagnosis Of Neurogenic Orthostatic Hypotension In Idiopathic Polyneuropathy – Screening With Modified Active Stand Test And 24-hour Ambulatory Blood Pressure.

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Introduction: Polyneuropathy (PN) affects approximately 4% of the general population, with prevalence rising markedly with age. Autonomic dysfunction, particularly neurogenic orthostatic hypotension (nOH), is likely underdiagnosed in PN patients despite its recognized association with impaired quality of life, and increased morbidity and mortality. Conventional active stand testing may insufficiently capture clinically relevant orthostatic hypotension (OH), as activation of the skeletal muscle venous pump can attenuate or obscure orthostatic blood pressure (BP) reductions. This study investigated whether modifying the screening strategy to include early or delayed BP drops during active stand testing and abnormal 24-hour ambulatory BP monitoring (24h-ABPM) enhances identification of nOH in patients with PN.

Method: Patients with orthostatic intolerance and confirmed small- and/or large-fiber PN were eligible for inclusion if screening demonstrated an abnormal active stand test and/or abnormal 24h-ABPM, defined as a non-dipping or reverse-dipping BP pattern. Eligible participants underwent standardized autonomic evaluation comprising tilt table testing, Valsalva maneuver, and deep breathing with continuous cardiovascular monitoring using the Task Force Monitor® (CNSystems Medizintechnik GmbH, Graz, Austria), in addition to Quantitative Sudomotor Axon Reflex Testing.

Results: Overall, 106 patients were included; 37% were female, and mean age was 70 years (range 25–85). Active stand testing demonstrated conventional OH in 11 patients, while 49 exhibited early or delayed BP drops and 60 had abnormal 24h-ABPM. Tilt table testing confirmed OH in 16 patients. Ten patients met criteria for nOH, defined by OH during tilt table testing combined with abnormal pressure recovery time during the Valsalva maneuver. Among patients with nOH, 60% were identified solely through the modified screening criteria and would not have been captured by conventional active stand criteria alone.

Conclusion: In patients with PN and orthostatic intolerance, modifying the screening strategy to incorporate early or delayed orthostatic BP drops and abnormal 24h-ABPM enhanced detection of nOH. Conventional active stand testing alone substantially underestimate the burden of nOH in this population.

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P.61 - Assessment Of Orthostatic Sympathetic Reactivity By Superficial Vein Imaging

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Introduction: Assessment of sympathetic nervous system function remains challenging in routine clinical practice. Because venous capacitance vessels contain most of the circulating blood volume and are strongly regulated by sympathetic activity, orthostatic stress should induce measurable superficial venoconstriction. This study evaluated whether superficial vein caliber analysis could provide a simple marker of sympathetic reactivity.

Methods: Eight healthy volunteers underwent measurements in the supine, seated, and standing positions. Superficial veins of the anterodistal forearm, maintained at heart level, were visualized using the AccuVein® device (LSO Médical, Loos, France), a device designed to assist venous cannulation. The proportion of visible venous surface area relative to the total analyzed surface area was quantified in each posture. Sympathetic activation was assessed using the low-frequency/high-frequency (LF/HF) ratio derived from RR-interval spectral analysis.

Results: Orthostatic stress induced a significant increase in LF/HF ratio in the standing position compared with both supine and seated positions ($p < 0.05$), whereas no difference was observed between supine and seated postures. Superficial vein measurements showed a progressive reduction in venous surface area from supine to seated and standing positions (supine: 0.347 ± 0.021; seated: 0.281 ± 0.016, $p < 0.01$; standing: 0.197 ± 0.018, $p < 0.001$). The decrease in visible venous area was consistent with sympathetic venoconstriction induced by orthostatic challenge.

Conclusions: Superficial vein caliber analysis using AccuVein detected posture-related venoconstriction associated with sympathetic activation during orthostatic stress whereas LF/HF differed only in the standing position. This simple, non-invasive approach may represent a practical tool for assessing sympathetic reactivity and deserves further evaluation in larger populations and in patients with autonomic disorders.

P.62 - Investigating The Cause Of Chest Pain In Postural Orthostatic Tachycardia Syndrome Using Cardiac Magnetic Resonance Imaging

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Background: Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by an excessive heart rate increase (≥30 bpm) within 10 minutes of standing and predominantly affects women of childbearing age. Chest pain is a common and debilitating symptom in POTS, yet its underlying mechanism remains unclear, often leading to patients' experiences being invalidated. Coronary microvascular dysfunction is common in women who experience chest pain but do not have coronary artery disease. Our study used cardiac magnetic resonance (CMR) imaging to assess whether impaired myocardial perfusion also contributes to chest pain in POTS.

Methods: To date, female patients with POTS and chest pain (n=26, 32±10 years) and age- and sex-matched healthy controls (n=7, 31±9 years) have undergone CMR imaging. Patients underwent a “stress” scan with adenosine infusion to dilate the coronary arteries and increase cardiac demand. Semi-quantitative perfusion analysis was performed using cvi42 software to calculate the myocardial perfusion reserve index (MPRI), defined as the ratio of stress to rest myocardial blood flow velocity. Left ventricular myocardial segments were assigned to the left anterior descending (LAD), right coronary artery (RCA), or left circumflex (LCX) territories. MPRI values of the myocardial segments were averaged by coronary territory and globally. Normality of the data distribution was assessed using the Shapiro-Wilk test. Comparisons between POTS patients and controls were then performed using the Student’s t-test, with data reported as mean±SD.

Results: MPRI did not differ between POTS patients and controls globally (1.50±0.39 vs. 1.75±0.30; p=0.13) or by coronary territory, including LAD (1.32±0.40 vs. 1.60±0.50; p=0.12), RCA (1.54±0.45 vs. 1.78±0.30; p=0.19), and LCX (1.59±0.46 vs. 1.81±0.23; p=0.23).

Conclusion: Preliminary findings from this ongoing study show lower MPRI in patients with POTS and chest pain compared with healthy controls, but the difference is not statistically significant. The consistent reductions across all coronary territories, along with lower-than-normal MPRI in POTS, warrant further investigation in a larger cohort to determine whether coronary microvascular function contributes to chest pain in POTS.

P.63 - Choline Precursor Supplementation Improves Excitatory/inhibitory Homeostasis Experimental Autism Model

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and restricted, repetitive behaviors. Disruption of excitatory/inhibitory (E/I) homeostasis is considered a central neurobiological mechanism underlying ASD. Because cytidine diphosphate-choline (CDP-choline) and uridine monophosphate (UMP) support membrane phospholipid synthesis, synaptic maturation, neurotransmission, and neuronal plasticity, we investigated whether perinatal supplementation with these membrane precursors could restore E/I balance in a valproic acid (VPA)-induced rat model of ASD.

Methods: Pregnant Wistar rats received sodium valproate (600 mg/kg, i.p.) on gestational day 12.5. CDP-choline or UMP supplementation (5 mg/mL in drinking water) was administered from gestational day 14 until weaning. Glutamate and GABA concentrations were quantified in the prefrontal cortex (PFC), hippocampus (HC), and cerebellum (CB) of male and female offspring at postnatal day (PND)22 and/or PND46. The glutamate/GABA ratio was calculated as an index of regional E/I homeostasis.

Results: Prenatal VPA exposure shifted the glutamate/GABA balance toward excitation in multiple ASD-related brain regions, with marked region-, sex-, and developmental stage-dependent differences. Both membrane precursors significantly attenuated these alterations. In male offspring, both CDP-choline and UMP restored the elevated glutamate/GABA ratio in the PFC at PND22 and PND46. In the cerebellum, both treatments normalized the persistent E/I imbalance observed at PND46. The hippocampus showed the strongest response: UMP completely normalized the elevated glutamate/GABA ratio at PND22, whereas CDP-choline produced a partial but significant correction. Female offspring demonstrated a similar pattern. VPA markedly increased glutamate/GABA ratios in the PFC, HC, and CB at PND22, whereas both treatments significantly restored E/I balance. Again, hippocampal normalization was most pronounced following UMP supplementation.

Conclusion: These findings demonstrate that perinatal choline precursor supplementation effectively restores excitatory/inhibitory homeostasis across multiple brain regions implicated in ASD. The most robust normalization was observed in the hippocampus, with particularly pronounced improvements at PND22. These results suggest that membrane precursor supplementation may represent a promising strategy for correcting neurochemical alterations associated with ASD.

P.64 - Abdominal Binders To Treat Orthostatic Hypotension In Parkinsonian Syndromes: A Randomized, Double-blind, Crossover Phase Ii Trial

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Introduction: Orthostatic hypotension (OH) is a frequent, debilitating non-motor feature of Parkinson's disease (PD) and Parkinson-variant multiple system atrophy (MSA-P), whose pharmacological treatment often remains limited by concomitant supine hypertension.

Methods: To investigate the efficacy of elastic abdominal binders for treating OH associated with parkinsonism, people with MSA-P or PD and neurogenic OH were enrolled in a randomized, double-blind, crossover phase-II trial. Participants wore both an abdominal versus placebo binder on two different days (separated by a 1-day interval), preceded and followed by a 5-day open-label home phase (first without, and afterwards with wearing the abdominal binder). Primary endpoint was change in Δmean BP at third minute of head-up tilt (HUT) after wearing the abdominal vs. placebo binder for 2 hours. Secondary endpoints included changes in absolute and further ΔBP values during HUT and active standing test in the clinic and at home, symptom burden as assessed by the Orthostatic Hypotension Questionnaire (OHQ), and biomechanical gait parameters measured by wearable motion-sensors (Portabiles HealthCare Technologies®). Cardiovascular autonomic function tests were performed with CNSystem's Task Force Monitor®. Paired-t-test results are reported as mean difference (±SD; 95% CI).

Results: Seventeen participants (n=6 MSA-P, n=11 PD; 71% male) with a median age of 68 and disease duration of 5 years were included. Upon HUT, similar BP profiles were observed when wearing the abdominal versus placebo binder (mean difference in primary endpoint: +2.0 [±12.1; -4.2, 8.2] mmHg, p=0.248). During home measurements, wearing the abdominal binder reduced the three minute active standing Δ mean and systolic BP fall at noon (+4.0 [±5.9; 0.7, 7.2] mmHg, p=0.010; +5.9 [±10.1; 0.3, 11.5] mmHg, p=0.020) without increasing supine BP levels, while also reducing the overall orthostatic symptom burden (OHQ total score -8.7 [±12.0; -15.4, -2.1]; p=0.007). Analyses of laboratory- and home-based gait parameters showed comparable results between wearing the abdominal versus the placebo or no binder.

Conclusion: While no acute changes in orthostatic hemodynamic responses were observed, these findings suggest that abdominal binders may serve as an effective and practical non-pharmacological measure to alleviate OH and reduce its burden in the daily life of people with MSA-P and PD.

P.65 - Use Of Midodrine For Orthostatic Hypotension In A Homeless Patient With Schizophrenia On Long Acting Injectable Paliperidone.

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Background: Orthostatic hypotension (OH) is a recognized adverse effect of antipsychotic medications, including long-acting injectable (LAI) paliperidone, resulting from α_1-adrenergic receptor blockade. Management is particularly challenging in socially vulnerable populations such as individuals experiencing homelessness. Although midodrine is an established pharmacologic agent for symptomatic OH, its use in LAI antipsychotic-induced OH in patients with schizophrenia has not been previously reported.

Case Presentation: A 47-year-old homeless male with schizophrenia, stabilized on paliperidone palmitate 234 mg intramuscularly every 4 weeks, presented with recurrent lightheadedness, dizziness, and near-syncope upon standing. Orthostatic measurements confirmed a systolic blood pressure drop from 116/74 mmHg supine to 92/58 mmHg standing, with heart rate rising from 82 to 101 bpm. Cardiac and neurological evaluations, electrocardiogram, and metabolic panel were unremarkable. Nonpharmacologic interventions were insufficient, and a trial of atomoxetine 36 mg daily yielded no improvement. Midodrine was initiated at 5 mg twice daily and titrated to 10 mg twice daily, resulting in marked symptomatic improvement and near-normalization of orthostatic measurements (supine 122/78 mmHg, standing 112/74 mmHg). No adverse effects were observed.

Outcome: At 19 months of follow-up, the patient remains on midodrine 10 mg twice daily with sustained symptom resolution and no side effects. He has returned to daily activities without functional limitation, and paliperidone therapy continues unchanged with stable psychiatric control.

Discussion: This case demonstrates the safe and effective use of midodrine for LAI antipsychotic-induced OH in a patient with schizophrenia experiencing homelessness. Current psychiatric guidelines recommend nonpharmacologic strategies and fludrocortisone for antipsychotic-associated OH but do not address midodrine. Cardiology and family medicine guidelines endorse midodrine for symptomatic OH broadly, yet no prior reports have evaluated its use specifically with LAI antipsychotic therapy. This case adds to the limited literature on autonomic management in psychiatric populations and underscores the importance of routine orthostatic monitoring and individualized intervention in patients with severe mental illness.

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P.66 - Effects Of Recumbent Isometric Yoga On The Postural Orthostatic Tachycardia Syndrome Of Patients With Myalgic Encephalomyelitis/chronic Fatigue Syndrome

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Introduction: We have demonstrated that the regular practice of recumbent isometric yoga reduced the fatigue of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Some patients with ME/CFS have postural orthostatic tachycardia syndrome (POTS); however, the effects of recumbent isometric yoga on orthostatic cardiovascular responses and whether recumbent isometric yoga improves POTS remain unknown. Therefore, this study investigated the effect of recumbent isometric yoga on the orthostatic cardiovascular response of patients with ME/CFS.

Methods: Ten adult patients with ME/CFS performed recumbent isometric yoga for 12 weeks. Changes in their systolic blood pressure (SBP), diastolic blood pressure (DBP), and the pulse rate (PR) during an active standing test were compared before and after the 12-week regimen.

Results: Among the 10 patients, 8 manifested a normal orthostatic response and 2 manifested POTS before the yoga intervention. Patients who manifested a normal orthostatic response before yoga also manifested the normal orthostatic pattern after the yoga intervention. In contrast, the two patients who manifested POTS before the regimen showed a normal orthostatic response after completing the yoga intervention.

Conclusions: This study demonstrated that the patients who manifested POTS and performed recumbent isometric yoga for 12 weeks had a reduced increase in PR after standing up, suggesting that recumbent isometric yoga would be useful as an adjunctive non-pharmacological intervention for improving POTS in patients with ME/CFS. This finding should be confirmed in a larger number of cases.

P.67 - Are Lower Limb Venous Compliance And Calf Muscle Pump Function Associated With The Heart Rate Responses To Standing In Postural Orthostatic Tachycardia Syndrome?

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Introduction: Postural orthostatic tachycardia syndrome (POTS) is a debilitating form of orthostatic intolerance defined by excessive increases in heart rate upon standing. This study tested the hypothesis that augmented lower limb venous compliance and diminished calf muscle pump function in POTS, reduce venous return and contribute to characteristic exaggerated heart rate response.

Methods: Sixteen patients with a clinical diagnosis of POTS (14 female) and 15 age- and sex-matched healthy controls (age 28±8 vs. 29±12 years, p=0.632; body mass index 24±4 vs. 23±2 kg·m2, p=0.414 ; Malmö POTS score 70±16 vs. 10±11 au, p<0.001) were recruited. Supine calf volume (strain-gauge plethysmography) and great saphenous vein (GSV) cross-sectional area (CSA, duplex ultrasound) were measured during a 60-mmHg thigh cuff inflation-deflation protocol. Calf (whole limb) and GSV (single vein) compliance were derived from the pressure-volume and pressure-CSA relationships during gradual cuff deflation. During a 10-minute active stand test, calf volume (air plethysmography) and heart rate (electrocardiogram) were measured. Muscle pump function was determined using air plethysmography by assessing the lower limb venous ejection fraction during a single step and ambulation (10 steps).

Results: Supine calf (p=0.303) and GSV (p=0.404) compliance were not different between the POTS and control groups. During standing, the calf volume (77 ± 21 mL vs. 73 ± 15 mL, p=0.614), single-step lower limb venous ejection fraction (49 ± 14% vs. 59 ± 19%, p=0.128) and ambulatory ejection fraction (51 ± 17% vs. 64 ± 19%, p=0.083) were also not different between the POTS and control groups. No significant correlation was observed between the heart rate response to standing and either supine calf or GSV compliance and muscle pump function for either group (all p>0.05).

Conclusion: Lower limb venous compliance and muscle pump function were not determinants of the exaggerated heart rate response to standing in these patients with POTS. These findings suggest that alternative mechanisms such as dynamic venous reactivity, impaired sympathetic venoconstriction, or central blood volume redistribution may play a more prominent role in orthostatic tachycardia. The trend towards reduced calf venous ejection fraction in POTS warrants further investigation in a larger cohort.

P.68 - Looking Beyond The Burst: Altered Sympathetic Action Potential Recruitment Following Spinal Cord Injury

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Spinal cord injury (SCI) is associated with impaired autonomic and sympathetic regulation; however, how SCI alters the organization of sympathetic nerve activity (SNA) remains incompletely understood. SNA is traditionally quantified using burst-based measures, which describe the occurrence and morphology of sympathetic bursts but provide limited information regarding the underlying action potentials (APs) that generate them. Since sympathetic bursts represent the summed activity of multiple APs, we used a wavelet-based approach to characterize sympathetic AP activity following high-thoracic SCI. Multiunit splanchnic SNA and blood pressure (BP) variables were recorded in Naive (n = 7) and T3-SCI (n = 7) rats. Sympathetic bursts and AP recruitment within bursts were quantified using a wavelet-based approach. Burst characteristics, AP metrics, and BP variables were quantified from one-minute baseline recordings. Data are presented as mean ± SD. Burst incidence was similar between Naive and SCI animals (174.8 ± 43 vs. 159.2 ± 39 bursts/300 heartbeats, $p = 0.49$), as was burst width (114 ± 8 vs. 103 ± 8 ms, $p = 0.31$). However, SCI animals demonstrated reduced burst height (0.05 ± 0.01 vs. 0.26 ± 0.20 V·ms, $p < 0.05$) and burst area (2.3 ± 0.7 vs. 3.5 ± 1.1 mV·ms, $p < 0.05$). Total APs were significantly reduced following SCI (1625 ± 558 vs. 2812 ± 450, $p < 0.001$), accompanied by a reduction in AP frequency (23 ± 3 vs. 51 ± 8 Hz, $p < 0.001$). AP latency was unchanged between groups (69 ± 14 vs. 69 ± 10 ms, $p = 0.90$). Importantly, the proportion of APs occurring within sympathetic bursts was significantly reduced in SCI animals (63 ± 10.8% vs. 75 ± 5.8%, $p = 0.02$), indicating altered organization of sympathetic firing. No significant differences were observed in HR, MAP, systolic BP, or diastolic BP between groups. Overall, T3-SCI alters sympathetic AP recruitment and synchronization despite preserved burst incidence. Wavelet-based analysis revealed fewer APs, lower AP firing frequency, and reduced firing organization of AP activity within sympathetic bursts, providing new insight into alterations in sympathetic neural organization following SCI that are not readily apparent from conventional burst-based measures.

P.69 - Cardiovascular Dysautonomia And Cognitive Fluctuations In Neuronal Alpha-synuclein Diseases

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Introduction: Cognitive fluctuations (CFs), defined as spontaneous and time-varying alterations in cognitive abilities, are a hallmark of Lewy body dementias (LBDs), including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), and represent a core clinical diagnostic feature of DLB. Autonomic dysfunction can be prodromal in LBDs, presenting with clinical heterogeneity, invariably affecting functional independence and quality of life.

Recent studies suggested a relationship between dementia and cardiovascular dysautonomia (CVDys), although underlying mechanisms are still unclear: the complex interplay between dysautonomia and cognition raises the possibility that CVDys may contribute to the occurrence and severity of CFs in LBDs.

Methods: We conducted a cross-sectional, observational, single-center study to investigate the prevalence of CVDys and CFs and to explore their potential association in patients with PD, PDD, and DLB. Demographic and clinical data were collected, focusing on motor and non-motor symptoms, dysautonomia-related manifestations, and CFs. Participants underwent cardiovascular autonomic assessment including head-up tilt test (HUTT) and 24-hour ambulatory blood pressure monitoring (24h-ABPM), and validated scales and questionnaires (MDS-UPDRS, NoMoFA, ESS, PDSS-2, OHQ, CAF, ODFAS, MoCA) were administered.

Results: Eighty-eight patients were enrolled, and 56 completed the study protocol. Neurogenic orthostatic hypotension (nOH) was identified in 54.5% of patients during HUTT, although only 18.0% reported nOH-related-symptoms. Supine Hypertension (SH) was detected in 61.3% showing inverted-dipping profile at 24h-ABPM. CFs resulted in 70.5% of patients. Patients with CVDys showed higher scores at CAF/ODFAS and reported more frequently CFs. Multivariate analysis demonstrated that higher nocturnal mean BP, higher nocturnal HR, and greater OH-related disability independently predicted CFs severity, accounting for 75% of variance in fluctuation scores.

Conclusions: The prevalence of both CVDys and CFs in our cohort were consistent with previous literature for DLB, while PD and PDD cohorts showed higher CFs prevalence than limited previous data. Individuals with CVDys experienced more frequent and severe CFs, while markers of both OH and SH emerged as independent predictors of CFs severity. These findings point toward a potential contributory role of CVDys in CFs and support and suggest that targeting CVDys may represent a promising strategy to improve fluctuating cognitive symptoms in patients with LBDs.

P.70 Oral Inflammation, Edentulism, And Autonomic Dysfunction In Hypertensive Complete Denture Wearers

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Introduction: Denture Stomatitis (DS) is a common inflammatory condition among complete denture wearers and may contribute to systemic alterations associated with cardiovascular disease. This study investigated the association of DS and Edentulism Duration with hemodynamic parameters, Blood Pressure, Heart Rate Variability (HRV), and Cardiovascular Risk in Normotensive and Hypertensive Edentulous Individuals.

Methods: In this observational case-control study, 45 complete denture wearers were allocated into three groups (n=15): Normotensive/Pre-Hypertensive Controls, Controlled Hypertensive (CH), and Uncontrolled Hypertensive (UH) individuals. All hypertensive participants were receiving antihypertensive therapy, including at least one diuretic. DS frequency and severity were assessed using the modified Newton classification. The duration was recorded by questionnaire. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were calculated as the mean of three measurements. HRV was assessed by electrocardiography and expressed as SDNN and RMSSD. Cardiovascular Risk was estimated using the Framingham Heart Study (FHS) score. Group comparisons were performed using ANOVA or Kruskal-Wallis tests with appropriate post hoc analyses. Associations were investigated using Kendall correlation and multiple linear regression.

Results: Significant differences were observed among groups for SBP (Control: 128±9.2; CH: 118±13.5; UH: 169±16.5 mmHg; $p<0.001$) and FHS score (Control: 10.0; CH: 12.9; UH: 30.6; $p<0.001$). Multiple regression analysis demonstrated that SBP was positively associated with DS frequency ($\beta=19.92$, $p=0.048$), DS Severity ($\beta=7.40$, $p=0.025$), and negatively associated with dental follow-up frequency ($\beta=-3.98$, $p=0.021$). Edentulism Duration was negatively associated with SDNN ($\beta = -0.624$, $p = 0.027$), indicating impaired autonomic modulation in individuals with longer edentulism.

Conclusion: Denture Stomatitis and prolonged edentulism are associated with hemodynamic and autonomic alterations, potentially contributing to increased cardiovascular risk, particularly in hypertensive complete denture wearers.

P.71 - Cardiovascular Autonomic Regulation During Sleep In Multiple System Atrophy: Impact Of Sleep-disordered Breathing And Cpap Treatment

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Background. Multiple System Atrophy (MSA) is rare, severe, and progressive neurodegenerative α-synucleinopathy characterized by marked autonomic dysfunction, particularly cardiovascular alterations, and motor symptoms. Sleep-disordered breathing (SDB), including obstructive sleep apnea (OSA) and nocturnal stridor, affects up to one-third of patients and is associated with increased cardiovascular risk. This study investigated cardiovascular autonomic control (CAC) during sleep in MSA, focusing on the impact of SDB and the effects of Continuous Positive Airway Pressure (CPAP) therapy.

Methods. Thirty patients with MSA were recruited at the Sleep Clinic of Pitié-Salpêtrière Hospital (Sorbonne University, Paris, France). All participants underwent polysomnography (PSG) on two consecutive nights. OSA and stridor were assessed from PSG recordings. CPAP was applied only to the treatment group (N=15) during the second night. The control group performed a new PSG on the second night without CPAP. CAC was evaluated by symbolic analysis of heart rate variability (HRV) from ECG recordings during wakefulness, non-REM (NREM), and REM sleep, using 0V% as an index of sympathetic modulation and 2LV%/2UV% as indices of parasympathetic modulation.

Results. Analysis of the entire cohort during the pre-intervention night demonstrated preserved physiological autonomic variability across sleep phases despite the underlying neurodegenerative condition: sympathetic predominance was observed during wakefulness and REM sleep, whereas parasympathetic modulation remained dominant during NREM sleep. The presence of OSA and/or stridor was associated with a shift in sympathovagal balance toward sympathetic predominance. Intra-subject comparison between the two PSG nights revealed significant changes only in the CPAP-treated group, characterized by increased parasympathetic modulation across all sleep stages (2LV%, Wake: 3.50±2.51 vs 6.68±3.39, $p<0.001$; NREM: 5.56±3.76 vs 7.50±3.41, $p=0.010$; REM: 2.32±2.02 vs 5.89±4.19, $p<0.001$).

Cnclusions. Consistent with previous observations in autonomic disorders, autonomic modulation during sleep appears preserved in MSA despite significant autonomic involvement. CPAP therapy may provide benefits beyond respiratory support, promoting a more favourable cardiovascular autonomic profile through enhanced parasympathetic modulation during sleep.

P.72 - Distinct Peripheral Sympathetic Autonomic Profiles In Msa-p And Msa-c: A Skin Biopsy And Cardiovascular Study

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Introduction: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by prominent autonomic dysfunction, with two motor subtypes, MSA-P (parkinsonian) and MSA-C (cerebellar): whether these subtypes differ in peripheral sympathetic involvement remains incompletely understood. The peripheral sympathetic nervous system can be assessed in vivo through skin biopsy, which permits quantification of sudomotor innervation. We hypothesized that MSA subtypes exhibit distinct patterns of peripheral sympathetic denervation that correlate with cardiovascular autonomic function.

Methods: All patients were evaluated at a single specialized center, to ensured methodological consistency and homogeneity. Clinical assessment included standardized rating scales (Unified Multiple System Atrophy Rating Scale—UMSARS, disease duration) collected at the time of study enrollment. Skin biopsies were obtained and processed for immunofluorescence quantification of Synapsin (pan-neuronal marker), VIP (vasoactive intestinal peptide, sympathetic cholinergic sudomotor), and TH (tyrosine hydroxylase, sympathetic adrenergic) fiber density around sweat glands, performed in a standardized manner by experienced technicians. Cardiovascular autonomic testing, conducted according to standardized protocols, included 10-minute head-up tilt-table testing (measuring changes in systolic and diastolic blood pressure and heart rate at 1, 3, and 10 minutes), deep breathing maneuver (expiratory-to-inspiratory ratio), and Valsalva maneuver (Valsalva ratio and blood pressure recovery time). All autonomic tests and clinical evaluations were performed on the same day at the study center, and results were recorded prospectively in standardized case report forms.

Results: Groups were comparable for disease duration (p=0.383) and UMSARS-I (p=0.566); UMSARS-II was higher in MSA-P (p=0.015). MSA-C showed lower absolute sympathetic innervation density at sweat glands compared to MSA-P, with consistent trends across all markers (Synapsin p=0.093, TH p=0.079, VIP/TH co-expressing fibers p=0.066). Functionally, MSA-C had higher neurogenic orthostatic hypotension (nOH) prevalence (71.4% vs 35.7%, p=0.021), exclusive early OH at 1 minute (23.8% vs 0%, p=0.012), and greater BP drop on tilt (ΔSystolic at 3 min: −16.2 vs −5.0 mmHg, p=0.036; ΔDiastolic at 7 min: −8.5 vs −2.1 mmHg, p=0.048). Neither E:I ratio nor Valsalva parameters differed between groups.

Conclusions: MSA-C shows greater peripheral sympathetic denervation than MSA-P, with preserved cardiac reflexes suggesting comparable central involvement and supporting skin biopsy as autonomic biomarker in MSA.

P.73 - Discrepancy Between Oscillometric Measure In Arm Vs Continuous Non Invasive Measurement Using Finger Photoplethysmography In Diagnosing Orthostatic Hypotension In Laboratory Setting

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Introduction: The finger cuff uses an infrared photoplethysmograph to detect arterial pulsations and maintain a constant finger blood volume using the volume-clamp method. Although it gives continuous signal, challenges involve accurate diagnosis of orthostatic hypotension (OH).

Objective: To compare continuous finger cuff and oscillometric blood pressure measurements for the diagnosis of orthostatic hypotension

Method: Patients presenting with symptoms suggestive of orthostatic intolerance, were recruited for the study. After obtaining informed consent and explaining the procedure, participants underwent a head-up tilt (HUT) test following 10 minutes of supine rest. Baseline blood pressure (BP) measurements were recorded simultaneously using an oscillometric arm cuff (UM-211) and a continuous finger photoplethysmography device (MLA382) on the contralateral hand. Participants were securely strapped to the tilt table, which was then elevated to 70°. Oscillometric BP measurements were obtained at 0.5, 1, 2, 3, and 5 minutes after tilting, while continuous beat-to-beat BP monitoring was performed throughout the 5-minute tilt period using finger photoplethysmography. For analysis, the average of the 10 lowest consecutive BP beats recorded within the first 3 minutes of tilt was calculated from the photoplethysmographic recordings and compared with oscillometric BP measurements for the diagnosis of orthostatic hypotension.

Result: The study was conducted on a total of 20 patients. Among these, 6 cases were true positives and 8 cases were true negatives considering oscillometry as the reference method. Discordant findings were observed in 6 cases: 4 cases yielded a positive result by finger photoplethysmography but a negative result by the oscillometric method, while the remaining 2 cases were negative by finger photoplethysmography and positive by the oscillometric method. Inter-method agreement was assessed using the Cohen's Kappa statistic, which yielded a value of 0.40.

Conclusion: Prior to adopting continuous non-invasive blood pressure monitoring as a substitute for conventional oscillometric measurements in clinical practice, internal validation is strongly recommended. Furthermore, the simultaneous application of both methods is advised to ensure the acquisition of accurate and reliable hemodynamic data.

TOPIC 07. Molecular And Systems-level Mapping Of Autonomic Circuits And Brain–body Integration

P.74 - Seasonal Variations And Air Pollutant Associations In Ischemic And Hemorrhagic Stroke: A Retrospective Analysis

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Aim/Objectives: To assess the relationship between clinical parameters of ischemic and hemorrhagic stroke and atmospheric quality factors, identify seasonal patterns of stroke incidence, and determine which pollutants independently predict stroke severity. (1,2).

Methods: A retrospective review included 729 patients (671 ischemic, 58 hemorrhagic) admitted between 1 January 2022 and 31 December 2023. Data from hospital electronic records provided demographics, laboratory values, imaging findings, and NIHSS scores. Daily mean SO_2, NO_2, $PM_{2.5}$, PM_{10}, O_3, and CO levels were obtained from the Southern Central Anatolia Clean Air Directorate. Spearman rank correlation assessed associations between pollutants and clinical variables, and chi-square tests compared seasonal frequencies. Analyses were performed with SPSS, with significance set at $p < 0.05$. Ethical approval was granted, and all patient data were anonymized.

P.75 - Transcriptomic Analysis Of Trpv1+ Kidney-innervating Spinal And Vagal Sensory Neurons

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Our research has been focused on defining the integration of afferent renal nerve (ARN) inputs within brain interoceptive circuits and the subtypes of ARNs. Ablation of TRPV1+ ARNs with capsaicin has been shown to be effective in lowering blood pressure in several preclinical neurogenic hypertension models highlighting TRPV1+ ARNs as a subtype of interest. Chemosensitive and mechanosensitive ARNs have been identified in the renal pelvis and close to glomeruli, however, the diversity of ARNs and their functional impact remain poorly understood. We used single cell RNA sequencing (scRNAseq) to investigate transcriptional subtypes of ARNs via the expression of neuronal injury markers, e.g., Atf3, 24 hours after axotomy by unilateral nephrectomy. We integrated the data from two experimental paradigms: 1) right-sided nephrectomy (axotomy), intact left side (intact-control), 2) right-sided nephrectomy (axotomy), left-sided kidney exposure without nephrectomy (incision-control), to compare left intact to right axotomized dorsal root ganglia (DRG) neurons. We also included the left and right nodose ganglia (NG) to investigate vagal ARNs. scRNAseq data were processed in R using a standard pipeline. Transcriptomic references for DRG and NG neuronal subtypes were applied to our identified clusters. An injury score was calculated per cell based on 524 injury-induced genes. Injury conditions were split into three groups, i.e., axotomy, incision, and intact, and compared for injury severity across subtypes to identify high injury scoring subtypes of interest. Clusters that were highly injured included thinly myelinated (Aδ) and unmyelinated (C-fiber) low threshold mechanoreceptors, several CGRP+ subtypes, nonpeptidergic nociceptors, nodose subtypes, and an unassigned cluster. We separated Trpv1+ cells that highly expressed Atf3 to identify differentially expressed genes between the axotomized and intact Trpv1+ ARNs. The potential sensory modalities of these cells and their alignment with ARN physiological responses in the literature were explored using differential gene expression analyses. Candidate subtypes are being validated by combining renal cortical tracing with immunohistochemistry and fluorescent in situ hybridization for CGRP+ subtypes and neurochemical markers. Ultimately, our goal is to identify genetic markers that can be used to selectively target ARNs to investigate their physiological roles and anatomy as well as transcriptional changes under pathophysiological conditions.

P.76 - Breathing As A Potential Interoceptive Signal For Decision-making Under Uncertainty

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Decision-making under uncertainty is a fundamental cognitive process strongly influenced by internal states such as stress and anxiety. Emerging evidence suggests that interoceptive signals, particularly breathing, shape perception, emotion, and cognition. However, whether breathing actively contributes to decision-making or merely reflects ongoing brain states remains unclear.

We have observed in a rodent decision-making task that breathing predicts the animal's upcoming choice (faster breathing predicts reward-seeking) and, in turn, task outcome influences breathing (omitting reward accelerates breathing). This suggests a mechanism where breathing could mediate the slow changes in decision policies.

To test a causal role for breathing, somatostatin-Cre (SST-Cre) mice were injected in the preBötzinger complex (preBötC) with a bidirectional optogenetic construct (BiPoles), enabling excitation or inhibition of the same neuronal population using different wavelengths of light. Breathing rate will be manipulated through wavelength-specific optogenetic control of SST neurons in the preBötzinger during task performance.

These results should help evaluate how breathing modulates behaviour when the outside world is risky, and therefore, turning to one's internal state is essential. Establishing such a link would provide new insight into how interoceptive signals shape behavioural strategies in uncertain environments.

P.77 - Characterising The Premotor Network Of Swallowing In Mice

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Introduction: Swallowing is a vital behaviour coordinated by a brainstem central pattern generator (CPG) to ensure efficient bolus transport while protecting the airway. Although the swallow CPG is localised to the medulla, the specific interneuron populations that organise this behaviour remain poorly defined. Emerging evidence suggests that ingestive motor circuits retain conserved visceral genetic signatures, including expression of paired-like homeobox 2b (Phox2b). Here, we investigate whether Phox2b-expressing ($Phox2b^+$) interneurons contribute to the swallow CPG and sought to characterise their functional role. Defining this circuitry is critical for understanding the vulnerability of swallowing to dysfunction (dysphagia), particularly in ageing and neurodegenerative disease.

Methods: Monosynaptic-restricted rabies virus tracing was used to may premotor networks by retrograde labelling from the thyroarytenoid (TA) muscle in neonatal mice, a key laryngeal adductor recruited during swallowing. To assess function, in vivo juxtacellular recordings were performed in the dorsal medulla of urethane-anaesthetised mice. Swallowing was evoked via intraoral water delivery, and neuronal firing patterns were analysed relative to swallow onset. Iontophoretic-dye labelling was used to reconstruct neuronal location, morphology, and Phox2b immunoreactivity.

Results: Rabies tracing revealed a discrete, genetically diverse premotor network spanning the brainstem to cervical spinal cord. Key populations included $Phox2b^+$ neurons in the nucleus tractus solitarius (nTS), $FOXP2^+$ neurons in the Kölliker-Fuse nucleus, $TPH2^+$ neurons in the caudal raphé, and cholinergic ($ChAT^+$) V0c neurons in C2–C5. Premotor axon collaterals projected to phrenic, infrahyoid, suprahyoid, and lingual motor pools, suggesting coordinated control of airway and orofacial effectors. Across ~90 juxtacellular recordings, five distinct activity profiles were identified: pre-swallow augmenting, pre-swallow burst, post-swallow augmenting, post-swallow burst, and swallow-inhibited. Functionally identified neurons were predominantly located along the caudolateral margins of the nTS, consistent with tracing data; however, only a small subset (2/13 recovered) expressed Phox2b.

Conclusion: These findings demonstrate swallowing is supported by a distributed, functionally diverse premotor network that integrates visceromotor and somatic pathways. $Phox2b^+$ neurons within the nTS likely contribute to this circuitry, although their precise functional role remains to be fully resolved.

P.78 - Nitric Oxide Synthase Activation In Nts Is Essential To Nmda Receptor-dependent Evocation Of Cough

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Introduction: Polymodal vagal sensory neurones that terminate in the mucosa of the large airways play essential roles in the production of cough. These 'cough receptors' project bilaterally from the nodose ganglia, are activated by protons and by mechanical stimulation, and terminate centrally in the medial (SolM) nucleus tractus solitarii. Blockade of N-methyl-D-aspartate (NMDA) receptors in SolM prevents coughing produced by activation of cough receptors. We hypothesized that nitric oxide synthase (NOS) activation and subsequent activation of cyclic guanosine monophosphate (cGMP) occur downstream of NMDA receptor activation at synapses within SolM and are essential for cough.

Methods: Male Hartley guinea pigs (1–2 months old, 250–350 g) were anaesthetised with intraperitoneal injections of urethane. Substances were microinjected into SolM, including NMDA, the NMDA receptor antagonist SDZ 220580, the NO synthase inhibitors Nω-nitro-l-arginine (L-NNA) and Nω-propyl-l-arginine (NPLA), the soluble guanylate cyclase (sGC) inhibitor 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), the phosphodiesterase 5 (PDE5) inhibitor zaprinast, and the NO donors sodium nitroprusside (SNP) and 3-morpholinosydnonimine (SIN-1). Respiration and cough were monitored using a pressure transducer introduced into the caudal trachea. In cough studies, the exposed trachea was superfused with warmed, oxygenated Krebs buffer containing 3 μM indomethacin. 100 μl aliquots of citric acid were introduced into the perfusate in ascending concentration to evoke reflex cough. After euthanasia and perfusion fixation, brainstems were recovered and processed before sectioning (20 μm) and staining for NADPH-diaphorase, which labels NOS-containing cells.

Results: NOS-expressing neurones were observed throughout the brainstem including a comparatively small population within SolM. Bilateral microinjections of NOS inhibitors into SolM markedly reduced citric acid-evoked coughing. Interestingly, citric acid-evoked coughing was not attenuated by inhibition of SolM soluble guanylate cyclase, and nor was it potentiated by inhibiting SolM cGMP-selective phosphodiesterase-5. Neither nitric oxide donors nor NOS inhibitors produced any effect on basal respiratory rate.

Conclusion: With respect to cough receptor-evoked coughing, we conclude that NO is an essential signalling molecule downstream of NMDA receptor activation in SolM, but does not act via sGC or cGMP. We speculate that enhancement of glutamatergic signalling by NO, perhaps through nitrosylation, is an essential component of cough receptor signal transduction within SolM.

P.79 - Brain-wide C-fos/fosb Mapping Of Intrinsic Drive And Social Dependency For Voluntary Exercise Using A Social Wheel Cage

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Introduction: Regular physical activity provides substantial health benefits, yet exercise motivation varies markedly among individuals. We hypothesized that voluntary exercise motivation comprises two distinct dimensions: intrinsic drive and social dependency. Although these behavioral characteristics can be quantified, their neural basis remains unclear. This study aimed to identify candidate neural networks associated with these motivational dimensions using brain-wide c-Fos/FosB mapping.

Methods: Male Long-Evans rats were housed in a custom-built social wheel cage with either a wire-mesh partition permitting social interaction or a black acrylic partition providing a non-social condition. Long-term wheel-running behavior was analyzed using generalized linear mixed models (GLMM) to estimate intrinsic drive and social dependency. Animals were classified into high- and low-drive groups and high- and low-social dependency groups. Following behavioral assessment, brains were processed for c-Fos/FosB immunohistochemistry, and activation patterns were compared across behavioral groups and environmental conditions.

Results: Behavioral modeling successfully dissociated exercise motivation into two relatively independent dimensions, intrinsic drive and social dependency. Brain-wide c-Fos mapping revealed differential activation in regions associated with motivation and social behavior, including the amygdala (BLA, CeA, and MeA), hypothalamus, striatum, dorsal raphe nucleus, rostroventral medulla, medial prefrontal cortex (mPFC), and nucleus accumbens (NAc), with distinct patterns across social conditions and behavioral phenotypes. In contrast, FosB expression showed robust activation particularly in the mPFC, NAc, BLA/CeA, and zona incerta, suggesting sustained neural activity associated with individual differences in exercise motivation. Together, these findings provide a brain-wide map of candidate neural networks underlying intrinsic drive and social dependency.

Conclusion: The social wheel cage paradigm characterizes exercise motivation using two complementary behavioral dimensions: intrinsic drive and social dependency. Brain-wide c-Fos/FosB mapping identifies candidate neural networks associated with these dimensions and provides a foundation for future circuit-level studies aimed at elucidating the neural mechanisms underlying individual differences in exercise motivation.

P.80 - Gaba Neurons In Nucleus Tractus Solitarius Are Positioned As Premotor Motor Hubs For Corticobulbar Laryngeal Control

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Upper airway's (UAW) thyroarytenoid muscle (TA) serves as a sphincter which must remain open during respiration, but closed during ingestion to prevent aspiration, making it critical for airway protection. Despite understanding of TA as the last line of defense against aspiration, there are limited circuit-based models for how this muscle is centrally controlled. Two major questions remain open: 1) which population of inhibitory pre-motor neurons project to TA-related lower motor neurons (LMNs) in nucleus ambiguus (nAmb) to achieve temporally precise inhibition and 2) how are TA-related motor neurons connected to upper motor neurons (UMNs) in motor cortex to elicit their functions related to the corticobulbar tract (CBT)? To answer these questions, we used a variety of viral tracing strategies. We hypothesized that GABAergic pre-motor neurons located in brainstem's nucleus tractus solitarius (nTS) provide CBT UMN-dependent spatiotemporal control of TA-related LMNs. Initial experiments injected TAs in C57BL/6J (C57) mice with the polysynaptic retrograde tracer, pseudo rabies virus (PRV), causing expression of red fluorescence (RFP) in TA-related motor circuits. After 24, 48, 72, and 96hrs, coronal brain slices containing motor cortex (MC), nTS, and nAmb were stained via IHC and imaged for RFP. nAmb demonstrated RFP+ labeling at all time points with nTS labeling beginning at 48hr. RFP+ cells were present in MC only at 72 and 96hrs. To confirm that nTS contains a population of GABAergic neurons related to TA function, transgenic mice expressing GFP in GABAergic neurons also received TA injections. A subset of GFP+ nTS neurons were also RFP+ 48hrs after injection. To confirm whether neocortex directly innervates nTS, a monosynaptic retrograde adeno-associated viral tracer (AAV) was injected into nTS of C57s to express GFP. GFP+ cells were present in layer 5 of neocortex. PRV injections in TA of C57 mice confirmed primary, secondary, and tertiary hierarchy of TA-related CBT neurons in nAmb, nTS, and MC, respectively. PRV injections in GAD mice reveal GABAergic nTS neurons involved in CBT. nTS injections of AAV in C57 mice confirm direct innervation from MC. Ongoing experiments test necessity and sufficiency of nTS premotor neurons in CBT control of TA regulation of UAW.

P.81 - Role Of The Olfactory Bulb And Gut Microbiota In Rats Social Synchronization During Wheel Running

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[Introduction] Regular exercise contributes to preventing lifestyle- and age-related diseases and decreased physical function; social factors could enhance motivation to exercise. Our previous research demonstrated that two rats synchronize their exercise behavior in a social environment. This study aimed to elucidate olfactory bulb and gut microbiome involvement in this synchronized behavior, as well as the associated cardiovascular responses to the exercise. [Methods] Sixteen 4-week-old male Long-Evans rats were divided into an olfactory bulbectomy (OBX) group (n = 8) and a sham-operated (Sham) group (n = 8). To evaluate social synchronization of exercise timing, pairs of rats were housed in two wheel-running cages separated by either a wire mesh or a black acrylic board partition. The wire mesh allows social contact whereas the black acrylic board prevents it. After the experiment, fecal samples were collected for microbiome analysis. Additionally, individual differences in exercise motivation were characterized by plotting extrinsic exercise motivation (social dependency), calculated using a generalized linear mixed model, on the vertical axis, and the amount of exercise, representing intrinsic motivation, on the horizontal axis. Finally, two types of running bouts were distinguished: “intrinsic exercise initiation” (starting exercise spontaneously) and “extrinsic exercise initiation” (starting exercise influenced by another individual), during which cardiovascular responses were evaluated. [Results] Significant exercise synchronization was observed in the Sham group ($p < 0.05$), but not in the OBX group. Furthermore, significant differences were observed in the Firmicutes/Bacteroides ratio and β-diversity of the gut microbiome between groups ($p < 0.05$). Moreover, mapping results showed significantly lower extrinsic exercise motivation in the OBX group compared to the Sham group ($p < 0.05$). Regarding cardiovascular responses, distinct response patterns in blood pressure and heart rate were observed during exercise and observation. [Conclusion] This study revealed that the olfactory bulb is involved in the induction of extrinsic exercise motivation through social synchronization in rats and that it affects the gut microbiome.
No conflicts of interest.

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P.82 - Possible Role Of Vip Neurons In The Sensory Vagal Pathway In Cardiovascular Regulation After Treadmill Exercise In Mice

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Introduction: It is well known that cardiac vagal afferent neurotransmission elicits autonomic reflexes, including efferent signals to the heart and vasculature that regulate cardiovascular function after exercise. In this study, we investigated whether vagal afferent nerves from abdominal organs, such as the digestive tract, as well as those from the cardiopulmonary system, are affected by exercise, and we report our findings.

Methods: The following mice were used for the experiments:
1. C57BL/6J mice for immunohistochemistry and bulk RNA-seq analysis of the nodose ganglion (NDG) after treadmill exercise.
2. VIP-Cre; tdTomato mice for neural circuit analysis in the NDG using tracers.
3. VIP-Cre mice for DREADD experiments to assess cardiac and autonomic function.
In Experiments 1 and 2, tissue sampling was performed under anesthesia induced by intraperitoneal administration of a ketamine–xylazine mixture. In Experiment 3, electrophysiological measurements were conducted under anesthesia induced by intraperitoneal administration of urethane.

Results: After treadmill exercise, the number of pERK-positive neurons in the NDG increased, and 227 genes showed significant differences compared with the resting control group, as shown in the heatmap. We confirmed the localization of one of these genes, VIP, in the NDG using VIP-Cre; tdTomato mice, and also demonstrated its co-localization with neural tracer–positive cells. Furthermore, when AAV-DIO-hM3D(Gq)-mCherry was introduced into the NDG of VIP-Cre mice followed by administration of CNO, bradycardia and hypotension were observed compared with the control vehicle group.

Conclusion: The vagal afferent pathway, which is altered after treadmill exercise in mice, may contribute to circulatory regulation. VIP neurons are considered potential key mediators of this pathway.

TOPIC 08. Autonomic Control Of Metabolism And Energy Homeostasis

P.83 - A Suspended Animation State Mimics Natural Torpor And Protects Against Ischemic Brain Injury

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Introduction: Torpor and hibernation are adaptive physiological states characterized by profound reductions in body temperature and metabolism that preserve organ function during environmental or metabolic stress. We previously demonstrated that chemogenetic activation of prostaglandin EP3 receptor-expressing neurons in the median preoptic nucleus (MnPOEP3R) induces a suspended animation state (SAS) that mimics natural torpor. Here, we aimed to characterize the neurological and metabolic alterations underlying SAS and evaluate its therapeutic potential in ischemic stroke.

Methods: Wake-sleep behavior during SAS was characterized by electroencephalogram (EEG) and electromyogram (EMG) recordings. Metabolic changes associated with our SAS model were assessed using plasma metabolomics and blood glucose measurements. Parabiosis experiments were performed to determine whether SAS-induced hypothermia is mediated by a circulating factor. Finally, SAS was evaluated as a therapeutic hypothermia strategy in a mouse model of transient ischemic stroke.

Results: Chemogenetic activation of MnPOEP3R neurons induced a reversible suspended animation state that closely resembled fasting-induced torpor. The reduction in body temperature was accompanied by marked suppression of EEG power, increased time spent in non-rapid eye movement (NREM) sleep, and suppression of REM sleep. SAS also induced a metabolic shift characterized by reduced glucose utilization and increased circulating branched-chain amino acids (BCAAs) and ketone bodies. In the parabiosis experiment, normothermic mice paired with SAS-induced animals exhibited a significant decrease in body temperature, supporting the presence of a circulating soluble factor that mediates hypothermia. In the transient ischemic stroke model, SAS significantly reduced brain edema, attenuated body weight loss, improved sensorimotor performance, and decreased mortality compared with normothermic controls.

Conclusion: SAS induced by the chemogenetic activation of MnPOEP3R neurons induces a reversible suspended animation state that reproduces key physiological features of natural torpor. Our findings suggest that SAS is associated with a circulating mediator of hypothermia and provides significant neuroprotection following transient cerebral ischemia, highlighting its potential as a novel therapeutic strategy for ischemic stroke.

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P.84 - Autonomic Recovery Markers Outperform A Pca-derived Autonomic Index In Predicting Relative Peak Power

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Autonomic cardiovascular regulation plays a vital role in the physiological response to exercise. Prior research suggests that reductions in heart rate variability (HRV) during exercise may indicate cardiorespiratory fitness. Recent studies highlight the role of central autonomic circuits in managing cardiovascular responses that limit high-intensity exercise. Despite these findings, it remains unclear whether an unsupervised composite autonomic index or specific recovery markers more accurately predict exercise performance. This study compared two approaches for predicting peak power output during incremental cycling. A group of 141 individuals performed cycling tests with RR-interval recordings. Relative peak power (Pmax/Wkg) was calculated by dividing peak power by body mass. Autonomic variables derived from RR intervals were assessed at rest, peak exercise, and passive recovery. Principal component analysis (PCA) was conducted on eight variables related to HRV suppression and recovery, with the first component used as an Autonomic Index. Additionally, a supervised regression model was built using two predictors that show strong associations with Pmax/Wkg: passive heart rate recovery (HRR_passive) and passive lnRMSSD recovery (lnRMSSD_final minus lnRMSSD_passive). Models were adjusted for age and sex. The PCA-based Autonomic Index explained 61.2% of the variance among selected variables but did not significantly predict Pmax/Wkg after adjustments ($\beta = 0.0628$, $p = .253$; $R^2 = 0.166$). Conversely, the supervised model performed better ($R^2 = 0.364$). Higher HRR_passive was associated with greater Pmax/Wkg ($\beta = 0.0266$ W/kg per bpm, $p < .001$), while greater residual lnRMSSD suppression from peak to recovery correlated with lower Pmax/Wkg ($\beta = -0.1231$, $p = .003$). Age negatively impacted performance, but sex was not a significant factor. The PCA Autonomic Index captured a consistent exercise-recovery dimension but did not independently predict peak power. In contrast, passive recovery markers, particularly HRR_passive and lnRMSSD recovery, showed clearer relationships with exercise capacity. This suggests that the ability to restore cardiovascular control and reactivate vagal modulation after exercise may be more informative for performance than resting autonomic tone or exercise-related HRV suppression alone. These findings support a shift from broad autonomic composite scores toward targeted recovery-based markers when developing autonomic indices of cardiorespiratory fitness.

P.85 - Purinergic Modulation Of Oxytocinergic Pvn–dmv Signaling In Liver-projecting Vagal Neurons

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Central insulin administration elevates circulating oxytocin (OT) levels, supporting a functional link between hypothalamic oxytocinergic neurons of the paraventricular nucleus (PVN), insulin signaling and hepatic glucose regulation. Furthermore, exogenous application of OT increases the excitability of dorsal motor nucleus of the vagus neurons (DMV)-liver projecting neurons, which provide hepatic parasympathetic output. However, whether endogenous contributes to the regulation of this circuit under physiological conditions remains unknown. We therefore hypothesize that OT acts as a neuromodulator of the PVN–DMV–liver vagal axis. To further investigate this pathway, we combined whole-cell electrophysiology recordings with optogenetics stimulation to characterize the functional of liver-projecting DMV neurons to activation of oxytocinergic PVN terminals. OxtCre/+ mice (B6;129S-Oxttm1.1(cre)Dolsn/J; JAX #024234) were crossed with Ai32 mice (B6.Cg-Gt(ROSA)26Sortm32(CAG-COP4*H134R/EYFP)Hze/J; JAX #024109) to generate offspring expressing the channelrhodopsin-2 (ChR2)-eYFP fusion protein in OT neurons in a Cre-dependent manner (CEUA ICB/USP #2945240424). To identify liver-projecting DMV neurons, OXTAi32 mice received fluorogold (FG) injections into the liver parenchyma 7 days before experimentation. FG-labeled liver-projecting DMV neurons were identified and recorded using voltage-clamp configuration in the presence of kynurenic acid (Kyn, 1mM) and broad spectrum P2 receptor antagonist, PPADS (10uM). PPADS application increased the peak amplitude of optogenetically evoked responses compared with Kyn alone (Kyn: -1.47 ± 21.3 vs. PPADS: 73.5 ± 66.3 pA, n=4/5, p=0.046, paired t-test). No significant changes were observed in mean and half-width of the responses. These preliminary findings suggest the presence of an inhibitory purinergic component in liver-projecting DMV neurons following activation of oxytocinergic PVN projections. The enhancement of the evoked response after P2 receptor blockade is consistent with the possibility that endogenous purinergic signaling exerts a net inhibitory influence on these neurons, an effect that is attenuated by PPADS. Financial support: FAPESP #2024/16941-3; #2024/02152-7

P.86 - Autonomic Control, Bone Metabolism And Body Composition Adaptations To Simulated Microgravity: The Daystar Project

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Introduction: Prolonged microgravity induces autonomic, metabolic, and skeletal adaptations that impair physical performance and increase health risks. Head-down tilt bed rest (HDT), a validated analog of microgravity, reproduces these effects, including autonomic nervous system (ANS) dysregulation, unfavorable body composition changes, and increased bone resorption. This study investigated the relationship between HDT-induced autonomic alterations, body composition, and bone metabolism focusing on the role of ANS in physiological deconditioning.

Methods: Sixty-five healthy participants were enrolled in ESA −6° HDT campaigns lasting 5, 21, or 60 days. Cardiovascular autonomic control was assessed at rest before HDT (BDC) and immediately after HDT (R0) using heart rate variability spectral analysis. Heart rate, low-frequency normalized units (LFnu), and high-frequency normalized units (HFnu) were used as indices of sympathetic and parasympathetic modulation. Body composition included body weight, fat mass, lean mass, and bone mineral content (BMC). Bone metabolism was evaluated through urinary C-terminal telopeptide of type I collagen (UCTX) and urinary N-terminal telopeptide (UNTX).

Results: At rest, HDT induced a significant increase in resting heart rate, that progressively rose with bed rest duration ($p < 0.001$). This was accompanied by increased LFnu and reduced HFnu in the 21- and 60-day protocols ($p < 0.001$), indicating sympathetic predominance and parasympathetic withdrawal.

Body weight decreased in a duration-dependent manner ($p < 0.001$), while lean mass declined after 21 days ($p < 0.01$) and further after 60 days ($p < 0.001$). The lean mass plus BMC to fat mass ratio progressively worsened (21 days, $p < 0.05$; 60 days, $p < 0.001$), indicating a shift toward a less favorable body composition.

Bone resorption markers increased significantly, with elevated UCTX after 21 and 60 days ($p < 0.001$) and UNTX rising at both time points ($p < 0.01$ and $p < 0.001$). Greater increases in LFnu were associated with larger reductions in body weight ($p = 0.0325$) and higher UCTX levels ($p = 0.035$).

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Conclusions: HDT-induced autonomic imbalance is closely associated with deterioration in body composition and increased bone resorption. Enhanced sympathetic modulation may contribute to metabolic and skeletal deconditioning during unloading, highlighting ANS as a potential target in long-duration spaceflight.

TOPIC 09. Gastrointestinal And Visceral Autonomic Regulation

P.87 - Npb/w Signaling System In The Gastrointestinal Tract: Altered Gene Expression And Inhibitory Effects On Colonic Motility In Diabetes

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Introduction: Diabetic gastroenteropathy is a frequent but underrecognized complication of diabetes mellitus (DM), associated with impaired gastrointestinal motility and neurochemical remodeling of the enteric nervous system. The neuropeptide B/W signaling system, consisting of neuropeptide B (NPB), neuropeptide (NPW), and their G-protein coupled receptor NPBWR1, has been implicated in autonomic and metabolic regulation, but its role in the gastrointestinal tract (GIT) remains poorly understood. This study aimed to characterize the distribution of the NPB/W signaling system along the GIT and to assess its modulation and functional relevance in experimental models of type 1 and type 2 DM.

Methods: Lean Zucker rats (controls, n=20), streptozotocin (STZ)-treated rats (type 1 DM model, n=40), and Zucker Diabetic Fatty (ZDF) rats (type 2 DM model, n=20) were studied at early (12-week old) and advanced (30- or 34-week old) stages of DM. Gene expression of NPB, NPW, and NPBWR1 was analyzed in the cardia, corpus, pylorus, duodenum, and colon using RT-qPCR. Protein expression and localization in the colon were assessed by Western blot and immunofluorescence. Functional effects were evaluated ex vivo by measuring acetylcholine-induced contractility of the distal colon in response to NPB and NPW.

Results: All components of the NPB/W signaling system were detected throughout the GIT, with marked region-specific differences. NPW expression was highest in gastric regions, whereas colonic expression was relatively low. Diabetes induced tissue- and stage-dependent alterations in gene expression, with more frequent and pronounced changes observed in STZ rats. In contrast, ZDF rats showed significant upregulation of NPBWR1 in the colon at both mRNA and protein levels. Immunofluorescence confirmed localization of NPB and NPW in enteric neurons and NPBWR1 in smooth muscle and epithelial cells. Functionally, both neuropeptides reduced acetylcholine induced colonic contraction in a concentration-dependent manner, with NPW exerting a stronger inhibitory effect.

Conclusions: The NPB/W signaling system is an integral component of gastrointestinal regulation and is differentially modulated by DM in a region- and stage-dependent manner. Its inhibitory effects on colonic motility, together with DM-induced alterations in receptor expression, suggest a potential role in the pathophysiology of diabetic gastroenteropathy and identify the NPB/W pathway as a promising therapeutic target.

P.88 - A Pilot Study Of Phosphorylated Alpha-synuclein Detection And Quantitation From Routine Colonic Biopsies In Patients With Parkinson's Disease

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Objective: To develop a novel method for the detection of phosphorylated alpha-synuclein (P-SYN) within superficial colon biopsies that can be obtained during routine colonoscopy.

Background: Parkinson's disease (PD) is characterized by progressive P-SYN deposition in the central and peripheral nervous system. Both the Braak hypothesis and the newer Brain/Body hypothesis of synuclein proliferation suggest the gastrointestinal tract as a major portal of disease. Although multiple autopsy studies have confirmed the presence of P-SYN within the GI tract, routine sampling of tissue through GI biopsies has never achieved satisfactory utility for clinical care

Methods: After consent, participants with a clinical diagnosis of suspected Parkinson's disease (PD) who were undergoing routine colonoscopy were asked to have four superficial 3-millimeter colon biopsies taken, two from the ascending and two from the descending colon. Samples were fixed, frozen, and sectioned into 50-micrometer sections. Tissue was stained for P-SYN and protein gene product 9.5. Complete confocal imaging of the slides at 20x magnification with 2 um Z-plane steps was taken through the tissue. Digital quantitative analysis of intra-axonal P-SYN deposition was measured (NerValence, CND Life Sciences).

Results: A total of 11 patients have completed colonoscopy (age 69.7±7.3 years, 6/11 female). P-SYN was detected in 8/11(73%) patients. In patients who reported constipation, 8/8 (100%) were P-SYN positive. Of the P-SYN negative cases, 1 was thought to have progressive supranuclear palsy (PSP), while 2 were considered possible PD without constipation.

Conclusions: In this pilot study, we demonstrate that P-SYN is present in routine colon biopsy samples from patients with PD and a history of constipation. Further study is required to define the number of biopsies, location of biopsies, sensitivity and specificity, but this preliminary data strongly suggests a potential role for immunostaining of colonic tissue in the evaluation of patients with or at risk for PD.

P.89 - "medulla-gut" Axis Imbalance Facilitates Postoperative Intestinal Pain And Motility Dysfunction In Mice

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Introduction: Postoperative intestinal pain and motility dysfunction represent a severe surgical complication that significantly shortens patient recovery time and imposes substantial impacts on both physical and mental health. Fortunately, our identification of a neuronal population in the rostral ventromedial medulla (RVM) region within the medulla capable of modulating both intestinal function and pain perception provides novel insights into investigating the role of the "Medulla-Gut" axis in these postoperative disorders.

Methods: Prospectively recorded perioperative data from patients undergoing intestinal surgery were retrospectively reviewed. In animal experiments, we employed chemogenetics, behavioral assays, electrophysiology, Neuropixels, single-cell RNA sequencing, and RNAscope in situ hybridization to characterize the neuronal populations mediating intestinal pain and motility dysfunction.

Results: Our findings found that 11.4% of patients undergoing intestinal surgery developed chronic postsurgical pain (CPSP) and 18.0% exhibited persistent intestinal dysfunction. We have reported that GPER is a marker for GABAergic ON cells; furthermore, we found that this population of neurons is extensively activated in the mouse model of colorectal surgery. Then, we observed that chemogenetic activation of GPER-positive neurons induced dual pathophysiological alterations in mice: (1) development of visceral hypersensitivity and (2) prolonged intestinal transit time. Furthermore, ON cells achieve co-regulation of intestinal pain sensitivity and intestinal motility disorders through descending “dual projections” to the superficial laminae of the spinal cord dorsal horn (sensory transmission zone) and the anterior horn.

Conclusion: We have found that GPER-expressing neurons play a critical role in the comorbidity of chronic visceral pain and intestinal dysfunction following intestinal surgery. Moreover, we demonstrate the dual regulatory role of GPER-expressing neurons in simultaneously modulating visceral nociception and intestinal motor function. Our findings map the neural circuit architecture through which GPER-expressing neurons bidirectionally modulate the sensory and autonomic “dual systems” in a top-down manner, concurrently influencing the “dual functions” of nociception and gastrointestinal motility. Our findings can provide a robust theoretical foundation for intervening in the RVM to achieve comprehensive treatment of visceral pain comorbidities.

P.90 - Maternal Gut Dysbiosis Disrupts Enteric Nervous System Organization And Cortical Inhibitory Circuit Development In Offspring

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Introduction: Maternal gut microbiota is increasingly recognized as an important regulator of offspring neurodevelopment through microbiota–gut–brain axis signaling. However, the effects of maternal dysbiosis on the parallel development of enteric and cortical inhibitory circuits remain poorly understood. We investigated whether gestational disruption of maternal gut microbiota is associated with alterations in enteric nervous system (ENS) organization and cortical GABAergic interneuron development in offspring.

Methods: Maternal gut dysbiosis was induced in pregnant GAD67-GFP mice by oral vancomycin administration during gestation. Maternal and offspring microbiota were characterized using full-length 16S rRNA gene sequencing. Offspring were evaluated at postnatal day 14 for intestinal morphology, epithelial barrier integrity, ENS organization, and cortical inhibitory circuit development. GAD67-positive interneuron density and morphology were assessed in the somatosensory cortex, motor cortex, medial entorhinal cortex, and hippocampal CA1 region using three-dimensional neuronal reconstruction.

Results: Maternal dysbiosis significantly reduced microbial diversity and disrupted maternal–offspring microbial transmission. Dysbiotic offspring exhibited impaired intestinal development characterized by reduced crypt height, thinning of the muscularis propria, disrupted Claudin-1 expression, and reduced Auerbach's plexus area. In the brain, maternal dysbiosis induced region-specific alterations in cortical inhibitory networks. GAD67-positive interneurons in the somatosensory and motor cortices demonstrated reduced dendritic length, branching complexity, and total dendritic intersections, whereas interneurons in the medial entorhinal cortex and hippocampus were preserved. Interneuron density was selectively reduced in the motor cortex. Correlation analyses revealed associations between dysbiosis-associated microbial signatures, altered ENS architecture, and simplified cortical interneuron morphology.

Conclusion: Gestational maternal dysbiosis is associated with concurrent alterations in enteric and cortical inhibitory circuit development. These findings identify selective vulnerability of sensorimotor inhibitory networks and enteric neural architecture to maternal microbiota disruption and support a role for maternal microbial ecology in shaping offspring gut–brain developmental trajectories.

TOPIC 10. Development, Aging And Sex Differences In Autonomic Function

P.91 - Muscle Sympathetic Nerve Activity Across The Menopause Transition In Healthy Females: Role For Reproductive Hormones

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Introduction: Cardiovascular disease risk increases progressively across the menopause transition, a period characterized by marked changes in reproductive hormones. Given chronic elevations in sympathetic nervous system activity contribute to the development and progression of cardiovascular disease, we tested the hypothesis that efferent muscle sympathetic nervous system activity (MSNA) increases across the stages of the menopause transition and is associated with reproductive hormone levels.

Methods: MSNA (peroneal microneurography) was measured cross-sectionally in three groups of females free from acute and/or chronic diseases and categorized by menopausal stage: 1) premenopausal (n=14, 28±10 yrs, 19-48 yrs), 2) perimenopausal (n=8, 47±3 yrs, 42-51 yrs), 3) postmenopausal (n=7, 62±7 yrs, 53-70 yrs). Menstruating females were tested in the early follicular phase of the menstrual cycle and venous blood samples were obtained to assess reproductive hormone concentrations (i.e., follicle stimulating hormone, luteinizing hormone, estradiol, progesterone).

Results: MSNA burst frequency (p=0.046), incidence (p=0.046), burst area/min (p=0.005), as well as total activity (p=0.024) increased with menopause, with levels higher in post- compared with premenopausal females (post hoc frequency: p=0.042, incidence: p=0.048; area: p=0.005; activity: p=0.021). Notably, MSNA did not differ between pre- and peri- (post hoc frequency: p=0.380, incidence: p=0.292; area: p=0.628; activity: p=0.932), nor peri- and postmenopausal groups (post hoc frequency: p=0.233, incidence: p=0.300; activity: p=0.137), except for burst area/min which was higher in post- compared with perimenopausal females (post hoc area: p=0.020). MSNA burst frequency, incidence, burst area/min, and total activity were positively correlated with follicle stimulating hormone (frequency: r=0.494, p=0.010; incidence: r=0.443, p=0.023; area: r=0.565, p=0.003; activity: r=0.492, p=0.011;) and luteinizing hormone (frequency: r=0.457, p=0.019; incidence: r=0.432, p=0.027; area: r=0.450, p=0.021; activity: r=0.412, p=0.036), but not estradiol (p-value range 0.285-0.893) nor progesterone (p-value range 0.682-0.963).

Conclusions: Present data support a rise in MSNA with menopause that is associated with elevated follicle stimulating and luteinizing hormones, but not estradiol nor progesterone. Future mechanistic work is required to identify independent effects of reproductive hormones versus age on sympathetic nervous system activity among healthy females.

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P.92 - Effects Of Aging And Hypertension On Neurochemical Composition Of Vagal Sensory Ganglia

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Introduction: The sensory ganglia of the vagus contain a phenotypically diverse population of neurons linked to distinct sensory modalities of their projections. Those associated with mechanosensation (e.g. baroreflex) characteristically express tentonin 3 (TTN3) and other mechanosensitive ion channels. Other populations include nitrergic neurons expressing nNOS and peptidergic neurons producing CGRP, both implicated in sensory co-transmission. Our study set out to determine whether aging and arterial hypertension may affect distinct neuronal populations found in vagal ganglia.

Methods: Male spontaneously hypertensive rats (SHR) of juvenile (prehypertensive, 8–9 weeks), adult (early hypertensive, 12–18 weeks) and aged (persistent hypertensive, 46–60 weeks) groups (n=3 per group) were compared to age-matched Wistar–Kyoto (WKY) rat controls. Jugular and nodose ganglia were immunohistochemically labelled against PGP9.5, CGRP, nNOS, and TTN3. Ganglion area, total neuronal count, and relative number of each phenotype neurons were analysed in each age group.

Results: With aging the ganglion area increases and the density of neurons decreases. In the ganglia of aged SHR, the density of neurons is significantly lower compared to controls. In the vagal sensory ganglia, the average relative number of CGRP+ neurons was the lowest – 13-20 percent, nNOS+ – 34-36 percent, and TTN3+ was the highest – 60-61 percent. The number of CGRP+ neurons increased in the ganglia of aged animals. In the ganglia of aged animals, SHR had fewer CGRP+ neurons compared to WKY, with notable lateral differences within animals. The number of nNOS+ neurons increased with age in the SHR. The dynamics of the number of TTN3+ neurons with age differed between SHR and WKY.

Conclusions: Both age-related and hypertension-induced changes occur in the vagal ganglia. With aging (1) the total number of neurons decreases, but (2) the number of CGRP+ neurons increases. Hypertension accelerates (3) neuronal loss; (4) inhibits the increase of CGRP+ neuron population; (5) and specifically affects nNOS and TTN3 vagal afferent neurons over time. These data warrant further investigation into functional significance of found differences.

P.93 - Sex-specific Autonomic Dysregulation Of Cardiovascular And Ventilatory Functions Following Acute Irreversible Acetylcholinesterase Inhibition

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Introduction: Acute exposure to organophosphate pesticides, such as chlorpyrifos (CPF), leads to the irreversible inhibition of acetylcholinesterase (AChE), triggering a cholinergic crisis. While CPF neurotoxicity is well-known, the influence of sex as a biological variable on the autonomic control of cardiovascular and ventilatory homeostatic parameters remains poorly understood.

Methods: Male and female Wistar rats (n = 7-12 /group) received CPF (30 mg/kg, i.p.) or saline. After 24h, ventilatory variables (VT, VE, and fR) were recorded by whole-body plethysmography. Hemodynamic parameters (MAP and HR) were then monitored via a catheterized femoral artery. After recordings, blood samples were collected to assess plasma butyrylcholinesterase (BuChE) activity using the Ellman´s method. Data were analyzed by two-way ANOVA with Tukey's post-hoc (CEUA Nº 04/2024 and 17/2022).

Results: Acute CPF exposure was confirmed by a significant reduction in BuChE activity in both males (± 84.07%) and females (± 85.19%). Irreversible inhibition induced distinct sex-specific profiles: intoxicated males exhibited a significant reduction in tidal volume (VT: 1.14 ± 0.41 vs. control: 3.38 ± 0.41 mL.kg-1) and minute ventilation (VE: 138.3 ± 53.86 vs. control: 336.5 ± 53.86 mL.kg-1.min-1), with no changes in HR. Conversely, intoxicated females showed significant bradycardia (HR: 317.8 ± 20.75 vs. control: 344.0 ± 20.75 bpm) without ventilatory alterations. MAP and fR remained stable across all groups.

Conclusion: Our findings demonstrate that CPF-induced autonomic dysfunction is sex-dependent. While males are more susceptible to ventilatory mechanics impairment, females exhibit a selective vulnerability to cardiac chronotropic dysregulation. These results underscore the importance of sex-specific analysis in the physiological failure following autonomic chemical challenges.

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P.94 - Impact Of Age On Autonomic Symptoms And Quality-of-life In Individuals With Orthostatic Intolerance- Postural Orthostatic Tachycardia Syndrome (POTS) Vs. Postural Symptoms Without Tachycardia (pswt)

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Introduction: Individuals with Postural Orthostatic Tachycardia Syndrome (POTS) frequently present with severe autonomic symptom burden and poor health-related quality-of-life (HrQoL). Our understanding of symptoms and HrQoL in those with orthostatic intolerance (OI) who do not meet the strict heart-rate criteria for POTS, is poorly understood. While research has demonstrated regression of orthostatic tachycardia with aging, there are no age-based adjustments within the diagnostic criteria for POTS beyond ≤19 years. We compared autonomic symptoms and HrQoL in POTS compared to Postural Symptoms Without Tachycardia (PSWT); examining age-related effects on Delta heart-rate (DHR) and symptoms.

Methods: Consecutive patients undergoing OI assessment completed patient-reported outcome measures (PROMS) capturing autonomic symptoms and HrQoL. Between group comparisons utilised Chi-square for categorical variables and an independent t-test or Mann-whitney u-test for continuous variables as appropriate. Correlations between age, DHR, and PROMS were explored using Spearman's test. A secondary analysis was conducted utilizing age and sex-matching. Analyses used SPSS v29.0; significance set at $P< 0.05$.

Results: A total of 414 POTS and 151 PSWT participants were included (88.6% female in POTS vs. 89.4% female in PSWT; $P= 0.800$). Median age was lower in POTS (28 IQR 21–36) than PSWT (38 IQR 26–51; $P< 0.001$). Overall autonomic symptom burden (COMPASS-31) was similar between groups ($P= 0.349$), while those with POTS demonstrated worse OI (COMPASS-31 OI subdomain; $P = 0.005$) and HrQoL (EQ-Utility; $P= 0.019$) than PSWT. After age and sex-matching, these differences were no longer significant ($P> 0.05$). Weak-to-moderate negative correlations were seen between age and DHR ($r= -0.34$, $P< 0.001$) and age and total COMPASS-31 ($r =-0.11$, $P= 0.01$).

Conclusion: Comparable symptom burden and HrQoL in POTS and PSWT highlight limitations of DHR-based criteria. As orthostatic tachycardia declines with age, current diagnostic thresholds may require re-evaluation.

TOPIC 11. Emerging Concepts And Novel Perspectives In Autonomic Neuroscience

P.95 - Catecholamines In Sepsis: Pharmacological Insights And Clinical Applications - a Narrative Review

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Catecholamines, essential neurotransmitters and hormones, play a critical role in the body's physiological response to stress and are pivotal in the management of various clinical conditions, particularly in critical care settings. This narrative review delves into the pharmacological properties of catecholamines, including their mechanisms of action, pharmacokinetics, and pharmacodynamics. Key clinical applications of catecholamines, especially in the cardiovascular and immune systems, are highlighted, emphasizing their roles in modulating heart rate, vascular tone, and immune responses during critical conditions such as sepsis and septic shock. Additionally, the review explores catecholamines' immunomodulatory effects and their interactions with other therapeutic agents, such as corticosteroids, in the management of septic shock. Further research is suggested to optimize catecholamine usage and improve patient outcomes in critical care settings.

P.96 - Mapping The Autonomic Landscape Of Unpleasant Experiences Through Scr, Heart Rate, And Pupillometry

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Background: Unpleasantness is an understudied affective dimension, where the physiological correlates of experiences with materials considered unpleasant to see and touch remain poorly understood. We aimed to characterize autonomic responses by examining skin conductance response (SCR), heart rate (HR) and pupil dilation (PUP) across three sensory conditions (touch, visual, visual-touch) and affective states (pleasant, unpleasant, neutral) in humans. We investigated whether affective states could be discriminated by SCR, HR, and PUP measures, using a supervised machine learning framework grounded in functional data analysis.

Methods: Thirty participants were exposed to materials with simultaneous recordings of SCR (median, AUC, peak amplitude, latency), cardiac indices (mean HR, RR, RMSSD), and pupil dilation (AUC, plateau and peak response), as well as giving pleasantness ratings. State-trait anxiety (STAI) and attitudes towards touch (TEAQS) were also assessed using questionnaires. Friedman tests, post-hoc Wilcoxon comparisons (Benjamini-Hochberg correction), and Spearman correlations (FDR-corrected) were applied.

Results: SCR was strongly modulated by sensory condition across all indices (median, AUC, peak amplitude, latency: $p < 0.001$), and significant condition × affect interactions were observed (all $p < 0.001$). For HR we found a significant condition × affect interaction for RR interval ($p = 0.010$). Together, these show larger skin conductance and cardiac modulations in the touch modality and for unpleasant objects. PUP indices showed no significant effects of sensory condition, affect, or the interaction between the two (all $p > 0.05$). Machine learning showed that accuracy of affective prediction improved depending on the combination of physiological parameters and sensory modalities, being higher when combining SCR and HR indices in the tactile modality. Further, we found no correlation between these measures and neither for the anxiety state, nor anxiety trait, as well as no significant correlations between the physiological responses and TEAQ questionnaire scores.

Conclusion: SCR and HR both reflect autonomic responses to touch, visual, and the combined visual-touch conditions, but with differing sensitivity and prediction accuracy. However, pupil dilation did not differentiate conditions and valences. These findings contribute to identifying objective physiological markers of non-painful, unpleasant touch that could be used to better understand negative emotional reactions to sensory stimuli.

P.97 - Fructose Ingestion During The Peripubertal Period Increase Blood Pressure And Sympathetic Activity In Adult Male But Not In Female Rats

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Introduction: The consumption of fructose has risen markedly in recent decades, driven by increased intake of ultra-processed foods and sweetened beverages. Exposure to this dietary pattern during the peripubertal period, a critical phase of development, may cause persistent metabolic and cardiovascular alterations into adulthood. Thus, the aim of the present study was to investigate the cardiovascular changes in adult male and female rats that ingested fructose during the peripubertal period. Possible mechanisms and anthropometric alterations were also investigated.

Method: Holtzman rats of both sexes (P30) were randomly assigned to control (CT) and fructose (FR) groups. From P30 to P60, the CT group received water and standard rat lab chow (SD), while the FR group received, in addition, a 20% fructose solution (ingestion of approximately 18-20 ml/day/rat). From P60, all rats received only water and SD, and the experiments were conducted at P120. Mean arterial pressure (MAP) was recorded in awake rats before and after administration of hexamethonium (HEXA; 30 mg/kg body weight [b.wt.], IV).

Results: In males (P120, n = 8-9/group), there was no change in the body weight between CT and FR groups, but there was an increase in adiposity in the FR group (gonadal, FR: 0.58 ± 0.02, vs CT: 0.49 ± 0.04; retroperitoneal, FR: 0.50 ± 0.02, vs CT: 0.37 ± 0.01; mesenteric, FR: 0.30 ± 0.01, vs CT: 0.20 ± 0.02 g/100 g of b. wt.; $p<0.05$). Baseline MAP was higher in the male FR group (123 ± 4, vs CT: 108 ± 3 mmHg, $p<0.05$), as was MAP reduction after HEXA (-54 ± 4, vs CT: -42 ± 2 mmHg, $p<0.05$). Conversely, in females (P120, n = 8/group), the only observed change was an increase in mesenteric adipose tissue in FR groups (0.45 ± 0.04, vs CT: 0.29 ± 0.03 g/100 g of b. wt.; $p<0.05$).

Conclusion: The results demonstrate that peripubertal fructose exposure increases MAP only in adult male rats, an effect that appears to depend on greater sympathetic activity. The FR group of both sexes showed increased adiposity, although the increase was more pronounced in males.

P.98 - Heart Evoked Potential Modulation By Deep Brain Stimulation Of The Subthalamic Nucleus For Parkinson's Disease: Links To Interoception And Sympathovagal Tone.

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Introduction: Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN), used as a treatment for pharmacoresistant, advanced Parkinson's Disease (PD), has been shown to improve vasomotor baroreflex sensitivity. This is also reflected by changes in the low frequency (LF) component of heart rate variability (HRV) while on STN DBS, although its overall reported effects on HRV may vary. Neuronal populations in the STN encode cardiorespiratory activity, suggesting a role in interoception. Heart evoked potentials (HEP) are utilised as a metric of interoceptive deficits and their response to treatment in clinical populations. However, the effect of STN DBS on interoception and HEP in PD remains unexplored.

Methods: Simultaneous EEG and ECG was recorded in a cohort of 24 PD patients implanted with the Percept™ PC neurostimulator in the STN. Signals were acquired during quiet wakefulness while on DBS therapy ('ON DBS') and with the device switched off ('OFF DBS'). We utilised the MAIA scale (Multidimensional Assessment of Interoceptive Awareness -MAIA scores) to examine for interoceptive awareness. Analyses were performed in Matlab, including use of the BrainBeats toolbox.

Results: STN DBS increased absolute HEP amplitudes compared to those present when off stimulation, across all pooled EEG channels (ANOVA $p<0.001$), with a moderate effect size when channels with maximal modulation were examined (Cohen's $d= 0.51$, $p<0.001$ and CI: 0.2787 - 0.3115). Greater HEP modulation correlated to higher levels of interoception ($p<0.05$, Spearman's rho: 0.37-0.60).

Overall, STN DBS decreased LF power compared to when stimulation was switched off (ttest 'ON' vs 'OFF', $p = 0.0196$, CI: 0.0327-0.3751). A greater degree of LF power modulation correlated with greater HEP modulation ($p= 0.0284$, rho: 0.4568). This effect was driven by patients with an LF(nu) increase when ON DBS ($p<0.005$, rho: 0.603-0.803). There was no significant correlation between these parameters, for patients where LF(nu) decreased while on stimulation.

Conclusions: We note that there is a link between the HEP amplitude modulation, mediated by STN DBS, and interoception in PD. DBS-mediated changes in sympathovagal tone are also associated with HEP modulation. Our ongoing work investigates how this putative biomarker can help us further understand DBS therapies.

P.99 - Self-organized Criticality, Dragon Kings, Black Swans, And The Prediction Of Vasovagal Syncope

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Introduction: Vasovagal events occur across a spectrum, from minor events to severe episodes resulting in syncope. The intensity distribution of these events follows a power law, as described by the universal theory of self-organized criticality (SOC). Extreme SOC events may manifest as unpredictable "black swans" or predictable outliers called "dragon kings." This study aimed to characterize the nature of the most significant events leading to (near)syncope.

Methods: We analyzed RR-interval time series from eleven healthy individuals who experienced vasovagal (near)syncope during a head-up tilt test. Bradycardia sequences were evaluated based on their intensity (number of beats) to construct Zipf's distributions and calculate the regression coefficient (r). Following the latest three-step approach for identifying event types, we first compared Zipf's distributions with and without the vasovagal (VV) event. Next, we applied time rescaling, and finally, we refined the definition of bradycardia sequences.

Results: The first step failed to demonstrate vasovagal syncope as a dragon king (r without VV vs. r with VV: 0.98±0.00 and 0.98±0.00, respectively). The second step proved inconclusive, as time rescaling disrupted the power law distribution. However, the third step revealed that the largest events acted as outliers or predictable dragon kings, significantly altering the correlation coefficient of event distribution (r without vs. with outliers: 0.98±0.01 and 0.86±0.02, respectively, p=0.001).

Conclusion: Our findings suggest that vasovagal syncope represents a dragon king in a self-organized system poised at criticality. These results pave the way for predicting vasovagal syncope based on recent advancements in SOC theory.

P.100 - Autonomic Nervous System Dysfunction In Interstitial Lung Diseases: An Uncharted Territory

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Background: Autonomic nervous system (ANS) dysfunction is well-characterized in chronic obstructive pulmonary disease and asthma, yet its role in interstitial lung diseases (ILDs) remains largely unexplored. Preclinical evidence reveals that both sympathetic and parasympathetic pathways actively participate in pulmonary fibrogenesis. Macrophage-derived netrin-1 drives adrenergic nerve remodeling and noradrenaline-mediated fibroblast activation in idiopathic pulmonary fibrosis (IPF), with α1-adrenoreceptor antagonism improving survival in a longitudinal IPF cohort. Conversely, vagal TRPV1+ nociceptors exert antifibrotic effects by suppressing aberrant alveolar macrophage-driven neutrophilic inflammation. Pulmonary fibrosis also alters central respiratory neural network activity at the nucleus of the solitary tract and Pre-Bötzinger complex. Despite these mechanistic insights, clinical characterization of ANS dysfunction across the ILD spectrum is virtually absent.

Objective: To systematically map the existing evidence on ANS involvement in ILDs, including IPF, sarcoidosis, connective tissue disease-associated ILD, and hypersensitivity pneumonitis, and to identify critical knowledge gaps for future investigation.

Methods: A scoping review will be conducted following the PRISMA-ScR framework. PubMed, Embase, Web of Science, and Cochrane Library will be searched from inception to 2026 using terms combining autonomic dysfunction, heart rate variability, sympathetic/parasympathetic activity, vagal innervation, and neural remodeling with ILD subtypes. Eligible studies will include preclinical models, clinical observational studies, and translational investigations. Data will be synthesized narratively across three domains: 1. peripheral autonomic innervation and neural remodeling in fibrotic lungs; 2. clinical autonomic phenotyping (heart rate variability, COMPASS-31, tilt-table testing) in ILD patients; and 3. therapeutic neuromodulation strategies.

Results: Preliminary evidence suggests that ILD patients exhibit chronotropic incompetence, sympathovagal imbalance, and neurological manifestations including tremor and cognitive dysfunction. In sarcoidosis, HRV analysis reveals significant autonomic impairment independent of lung function stage. However, no study has systematically correlated autonomic parameters with ILD-specific outcomes such as forced vital capacity decline, diffusing capacity, or mortality.

Conclusions: This review will provide the first comprehensive framework of the limited evidence linking ANS dysfunction to ILD pathophysiology and clinical outcomes. With no autonomic parameter yet linked to disease outcomes, it remains hypothesis-generating, outlining a research agenda for autonomic phenotyping, biomarker discovery, and neuromodulation, including α1-adrenoreceptor blockade, whose therapeutic relevance in fibrotic lung diseases remains to be validated.

P.101 - Digital Pulp Function – Autonomic Fibres Control Unveiled By High Frequency Ultrasound Imaging

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The distal fingers and toes phalanxes pad is unique dermoto-neuro-vasculo-eccrine structure, arranged within connective and adipose tissue with dynamically adaptive interstitial fluid like spaces1, acting in synchrony to various external and internal physiological stimuli under autonomic nerve fibres control. Those, digital pulp effectors can be targeted to asses small fibre nerves function and dysfunction by well-known induced skin wrinkling test2.
This talk demonstrates a novel method and information about digital pulp structures and function in normal physiological as well as pathological conditions. High frequency ultrasound imaging could determine more reliable scoring system of water induced skin wrinkling test3 and can increase its diagnostic yield in length dependent small fibre peripheral neuropathies by including toes in the assessment4. Also, it adds further inside on induced digital pulp wrinkling underlying mechanisms5.

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P.102 - Relationship Between Depressive Symptoms, Quality Of Life, Cardiovascular Autonomic Control And Inflammation In Patients With Bipolar Disorder (preliminary Result Of "domino" Study)

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Introduction: Depressive episodes in bipolar disorder are associated with severe functional impairment, increased suicide risk and frequent treatment resistance. Identifying innovative therapeutic approaches targeting the neurobiological mechanisms underlying bipolar depression is a major objective of the ongoing PNRR-funded DOMINO study. Non-invasive neuromodulation techniques, including transcutaneous auricular vagus nerve stimulation (tVNS) and repetitive transcranial magnetic stimulation (rTMS), have shown promising results in treatment-resistant mood disorders. This study aims to compare the effects of these interventions on depressive symptoms, inflammatory status, cardiovascular autonomic regulation, and quality of life in patients with bipolar disorder with particular focus on the non-inferiority of tVNS compared with established treatments.

Methods: To carry out these preliminary analyses, the data available from the PNRR-DOMINO study were considered. Patients with bipolar disorder diagnosis experiencing a depressive phase were recruited at Policlinico Ospedale maggiore of Milan. Depressive symptoms were assessed using the Hamilton Depression Rating Scale and the Beck Depression Inventory-II, while quality of life was evaluated through standardized questionnaires. Cardiovascular autonomic control was evaluated through heart rate variability analysis during an active-standing test. Blood samples were collected to measure pro and anti-inflammatory biomarkers (TNF-α, IL-6, IL-10 and BDNF). Moreover, a group of healthy controls was also recruited for comparison of HRV parameters.

Results: Preliminary analyses explored the relationships among depressive symptoms, autonomic regulation, and inflammatory profile in 34 patients. Compared with healthy controls, patients showed significantly lower Total Power ($p<0.001$) and HFnu ($p=0.024$), indicating reduced parasympathetic modulation. TP was negatively associated with TNF-α ($\rho=-0.460$; $p=0.007$), IL-6 ($\rho=-0.599$; $p=0.0002$), and BDNF ($\rho=-0.375$; $p=0.032$), whereas heart rate was positively correlated with TNF-α ($\rho=0.583$; $p=0.0004$). Additionally, 2LV was negatively correlated with IL-6 ($\rho=-0.347$; $p=0.048$). No associations were observed between depressive symptom severity and inflammation.

Discussion: Preliminary findings suggest that bipolar depression is characterized by autonomic dysfunction associated with a pro-inflammatory profile, supporting the involvement of the brain-heart-immune system connection in disease pathophysiology. Neuromodulation may therefore represent a promising therapeutic strategy capable of targeting both depressive symptoms and biological disease mechanisms. Final analyses will clarify the effects of tVNS and rTMS on clinical outcomes and cardiovascular and inflammatory markers in pharmacoresistant bipolar depression.

P.103 - Heart Rate Fragmentation As A Marker Of Autonomic Function In Healthy Young Individuals: Insights From Graded Head-up Tilt Test And Controlled Breathing

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Heart rate fragmentation (HRF) is a novel approach within heart rate variability (HRV) analysis that characterizes rapid beat-to-beat irregularities in cardiac intervals. Increased HRF has been associated with aging, cardiovascular disease, mortality, and adverse cardiovascular outcomes. Although conventional HRV indices are widely recognized as markers of autonomic modulation, HRF has been suggested to reflect intrinsic sinoatrial node dynamics largely independent of autonomic influences. However, the physiological determinants of HRF in healthy individuals remain poorly understood. The present study investigated whether HRF changes in response to controlled autonomic challenges and examined its association with established HRV indices. Twenty healthy adults (29 ± 4 years) underwent ECG recordings during two autonomic maneuvers: a graded head-up tilt test, designed to progressively increase sympathetic activation and reduce vagal modulation, and controlled breathing at 0.1 Hz, a condition known to enhance cardiac parasympathetic activity while shifting respiratory oscillations to a lower frequency range. HRF indices were analyzed together with conventional time- and frequency-domain HRV measures and symbolic dynamics parameters. Associations between HRF and HRV metrics were evaluated using Spearman correlation analysis. Graded tilt induced a progressive decline in HRF indices, paralleling reductions in vagally mediated HRV measures. Among HRF metrics, the percentage of inflection points (PIP) exhibited a strong positive correlation with the 2UV% symbolic pattern (r = 0.74). During controlled breathing, parasympathetic modulation increased and respiratory oscillations shifted from the high-frequency to the low-frequency spectral range. Consequently, variables associated with higher-frequency dynamics (HF, 2UV%, PIP, and other fragmentation-related indices) decreased, whereas low-frequency measures (LF/HF, 0V%, and 2LV%) increased. These findings provide physiological evidence that HRF in healthy individuals is significantly influenced by cardiac autonomic modulation, particularly parasympathetic activity. The close relationship between HRF and vagally mediated HRV indices suggests that both metrics reflect overlapping aspects of cardiac parasympathetic regulation. The results challenge the concept of HRF as a purely intrinsic and autonomic-independent marker and indicate that HRF tracks vagal modulation through the high-frequency oscillatory content of the RR interval series. Further studies are needed to determine whether this relationship is preserved or altered under pathological conditions.

P.104 - The Analysis Of The Regional Cerebral Blood Flow Responses To Trigeminal Olfactory Stimulation And Their Nicotinic Cholinergic Regulation

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Olfactory dysfunction is an early symptom of Alzheimer's disease (AD). Basal forebrain cholinergic neurons, which degenerate in AD, project to the neocortex and olfactory bulb. Nicotinic acetylcholine receptors (nAChRs) in the brain play a crucial role in vasodilation in the neocortex induced by basal forebrain cholinergic activation or nicotine injection. Information about the sense of smell is conveyed by the olfactory nerve, or by the trigeminal nerve when irritating odors. We recently reported that olfactory nerve stimulation increases regional blood flow in the olfactory bulb, and the intravenous nicotine potentiates olfactory bulb blood flow responses. This study aimed to clarify 1) the effects of intranasal trigeminal stimulation on regional cerebral blood flow, 2) the effects of activation of nicotinic cholinergic transmission.
Using anesthetized artificially ventilated rats, regional blood flow in the olfactory bulb and frontal cortex was measured by laser Doppler flowmeter or laser speckle contrast imager. Arterial blood pressure was simultaneously recorded. Intranasal trigeminal nerve was stimulated electrically. Nicotine, a nAChR agonist, at a dose of 30 μg/kg was intravenously injected.
Intranasal trigeminal nerve stimulation increased blood flow in both olfactory bulb and frontal cortex with pressor response. In rats spinalized at the upper thoracic level, the intranasal stimulation did not elevate blood pressure and olfactory bulb blood flow, but increased blood flow in the frontal cortex. Intravenous injection of nicotine did not influence the olfactory bulb blood flow but augmented the increased blood flow in the frontal cortex following the intranasal trigeminal nerve stimulation.
The present study revealed that 1) stimulation of the intranasal trigeminal nerve itself did not affect the olfactory bulb blood flow while it increased blood flow in the neocortex, 2) activation of nAChRs did not influence the olfactory blub blood flow while it potentiated the neocortical blood flow responses to intranasal trigeminal nerve stimulation. These findings suggest that the olfactory information transmitted via the different neuronal pathways, olfactory and trigeminal nerves, is processed in different regions in the brain. Moreover, activation of nicotinic cholinergic transmission potentiates both olfactory neural pathways.

P.105 - Age-dependent Changes In Vasopressin Signaling And Urine Production In The Bat (carollia Perspicillata)

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Bats are widely studied because of their longevity. Many species of bat are known to live longer in captivity than in the wild. Our captive colony of Carollia perspicillata, Seba's short-tailed fruit bat, has members >15 years old. Bats offer other advantages as a model organism, including neuroanatomy and systemic physiology that closely resembles primates. We have detected changes in vasopressin neuron neuron number and size associated with functional changes in urine output in elderly Carollia relative to young adult Carollia. The immunohistochemicalchanges in vasopressin-ergic neurons in paraventricularnucleus (PVN), supraoptic nucleus (SON) and suprachiasmatic nucleus (SCN) together with changes in urine output based on a novel urine detection method suggest that Carollia can be a useful model for studies of the mechanisms underlying nocturia and polyuria and for studies of approaches to correct these age-related derangements.

P.106 - Exercise And Anxiety: Findings From An 8-week Randomised Control Trial Investigating Changes In Physiological And Perceptual Sensitivity To Hypercapnia

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Anxiety is an adaptive emotional state facilitating preparation, safety, and maintenance of homeostasis. While often characterised by cognitive features such as worry towards uncertain threats, anxiety is also accompanied by physiological symptoms such as tachycardia and altered ventilation patterns, which can themselves further exacerbate anxiety. Elevated pressure of blood carbon dioxide (PCO2) is a powerful anxiogenic stimulus that induces sympathetic arousal, increased ventilation and perceptions of breathlessness and anxiety. While the physiological and perceptual sensitivity to hypercapnia is often elevated in anxiety disorders (particularly panic disorder), this has not yet been systematically mapped in those with elevated (subclinical) levels of anxiety. Furthermore, exercise can be used to reduce anxiety symptoms and provides sympathetic arousal exposure, which may act to desensitise hypercapnic response. Here, we compared a group of moderately anxious individuals to low-anxiety controls, before randomising the anxious group into an 8-week intervention of either self-selected intensity aerobic or stretching exercise. We measured absolute cardiac and ventilatory responses to hypercapnia, as well as sensitivity (slope) against pressure of end-tidal CO2 (PETCO2). Additionally, we measured breathlessness and anxiety towards breathing responses to hypercapnia. Perceptions were mapped against physiological domains to determine the likely drivers of reactivity. Moderate-anxiety individuals displayed increased absolute breathing-related anxiety at rest and in response to hypercapnia, despite similar physiological measures to low-anxiety individuals. Additionally, the moderate group demonstrated specifically increased perceptual sensitivities to both respiration rate and tidal volume. Aerobic and stretching interventions both decreased absolute breathlessness and anxiety towards breathing during hypercapnia, without concurrent physiological changes. Notably, both interventions decreased perceptual sensitivity towards respiratory rate and tidal volume, shifting these slopes towards the low-anxiety groups levels. Resting heart rate variability did not differ between low and moderate-anxiety groups and was unaffected by either intervention. Overall, moderately anxious individuals exhibit increased perceptual, but not physiological, reactivity to hypercapnia, driven by sensitivity to mechanical changes in respiratory rate and tidal volume. An 8-week exercise intervention decreased perceptual sensitivity towards those seen in low anxiety. Despite differential exposures to autonomic nervous system output, both exercise modalities successfully modified the valence of physiological arousal signals alongside their anxiolytic effects.

P.107 - Auto-induced Cognitive Trance Modulates The Physiological Response To Stress

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Introduction: Previous studies on mindfulness meditation demonstrated benefits for mental and physical health, including reductions in allostatic load through effects on heart rate, blood pressure, cortisol, and immune function. Stress can be assessed through autonomic nervous system (ANS) activity, with acute stress associated with increased sympathetic and reduced parasympathetic activity. Physiological markers such as electrodermal activity, heart rate, respiratory frequency, and respiratory heart rate variability (RespHRV) can be used to estimate stress response, particularly stress reactivity and post-stress recovery. In line with these observations, we hypothesized that Auto-Induced Cognitive Trance (AICT) could reduce stress-related allostatic load in healthy individuals by improving hypothalamic–pituitary–adrenal axis regulation and autonomic regulation.

Methods: Twenty healthy participants, 10 men and 10 women, were followed using a multiple-baseline Single-Case Experimental Design (SCED) to account for individual trajectories and intra-individual variability in physiological responses. At each measurement point, participants were exposed to a repeated stress task (RMST), during which electrodermal activity, respiration, and cardiac activity were recorded to derive RespHRV and other physiological metrics. Seven blood and seven saliva samples were collected to assess biological stress markers. Participants also completed questionnaires assessing perceived stress, quality of life, interoception, and attachment style at the beginning and end of the protocol.

Results: Preliminary analyses revealed that, for mean skin conductance level, most participants showed a decrease in both stress-phase and post-stress recovery values following AICT introduction, suggesting an overall reduction in electrodermal activation rather than a selective improvement in recovery. For mean respiratory frequency, heart rate, and RespHRV, individual trajectories were more heterogeneous: some participants displayed improved post-stress recovery after AICT, whereas others showed opposite, stable, or fluctuating profiles according to AICT practice. Blood, saliva, and questionnaire data remain to be analyzed.

Conclusion: These preliminary findings suggest that AICT may modulate physiological stress regulation, particularly through reduced electrodermal activation. However, effects on post-stress autonomic recovery, especially as indexed by RespHRV, respiratory frequency, and heart rate, appear more heterogeneous. This study highlights the importance of considering physiological markers separately and supports the use of SCED to identify individual responses to AICT and other non-ordinary states of consciousness.

P.108 - Hydrocephalus & Consciousness: Autonomic And Arousal Gains After Shunting.

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Introduction: Prolonged disorders of consciousness (PDOC) involve disturbances of arousal–awareness coupling from dysfunction within brainstem–diencephalic arousal systems, thalamo-cortical networks, and central autonomic network (CAN). Identifying reversible failure within these circuits remains challenging. Following acute brain injury, secondary hydrocephalus is known to contribute to PDOC, but shunting decisions often rely on empirical clinical criteria. We hypothesized that ventriculoperitoneal (VP) shunting in PDOC patients with objective cerebrospinal fluid (CSF) circulation alteration, would improve arousal and modulate the autonomic nervous system (ANS).

Methods: We analyzed the first eight patients in our prospective Hydrocephalus & Consciousness HYCO study (clinicaltrialgov NCT05219331) presenting with PDOC as a results of an acute brain injury and cerebral hydrodynamic alteration demonstrated by mean of lumbar infusion study. Consciousness was assessed via the Coma Recovery Scale–Revised (CRS-R) before and 3 months after the shunt insertion. ANS was evaluated by continuous HRV recording (5 minutes in controlled conditions) and 24h ABP recordings pre and post VP shunting. Due to the small sample size and non-normal distribution, paired comparisons were performed using Wilcoxon signed-rank test.

Results: Mean CRS-R scores increased from 15.8±5.1 preoperatively to 18.3±5.1 postoperatively ($p<0.05$), indicating conditon associated with improved behavioral responsiveness. This behavioural gain was accompanied by a selective increase ($p<0.01$) in vagally mediated HRV indices (RMSSD, HF) and a reduction in LF/HF ratio, compatible with a shift toward greater vagal predominance and reduced relative sympathetic contribution. While macro-hemodynamic ABP metrics remained stable, shunting was accompanied by a reduction in heart rate from 83±9 to 73±10 ($p=0.012$).

Conclusion: Objective correction of CSF hydrodynamic dysfunction was associated with improved behavioral responsiveness and increased vagally mediated autonomic activity, supporting the hypothesis that hydrocephalus may reversibly disrupt coupled arousal–CAN in PDOC. Although HRV and ABP provide indirect measures of ANS function, their convergent changes after shunting are consistent with improved behavioral responsiveness and vagal predominance. These preliminary findings warrant further investigation. Ongoing FDG-PET analyses will determine whether autonomic and behavioral improvements co-localize with changes in CAN and arousal networks, helping clarify the links between CSF hydrodynamics, ANS regulation, interoception, and consciousness.

P.109 - Interoception In Hydrocephalus: Csf Hydrodynamics, Intracranial Baroreflex, And Autonomic Rebalancing By Shunting.

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Introduction: Hydrocephalus is a mechanobiological systems disorder in which altered cerebrospinal fluid (CSF) hydrodynamics subject brain structures to sustained mechanical strain. Modest increases in intracranial pressure (ICP) evoke proportional, reversible sympathetic responses, compatible with a pressure-sensitive intracranial autonomic reflex. Interoception, the sensing and regulation of internal bodily states, offers a framework for how these intracranial biomechanical signals modulate autonomic nervous system (ANS) and central autonomic network (CAN) function. We hypothesise that hydrocephalus-related autonomic changes reflect dysregulation of the ANS and CAN within this interoceptive framework, and that CSF drainage/shunting may mechanically modulate these pathways, biasing the ANS away from sympathetic dominance.

Methods: We synthesised: (1) animal and human ICP-manipulation experiments in which modest ICP elevation during infusion paradigms demonstrated a graded coupling between ICP, sympathetic nerve activity and arterial blood pressure (ABP); (2) a premature infant with post-haemorrhagic hydrocephalus studied with serial heart rate variability (HRV) before and after ventriculoperitoneal shunting; and (3) preliminary data from the HYCO study assessing HRV and ABP changes after shunting in patients with ventriculomegaly, altered hydrodynamics demonstrated by infusion study and disorders of consciousness. Observations were interpreted using HRV and ABP indices as indirect readouts of autonomic regulation within a putative interoceptive framework.

Results: Across experimental ICP-manipulation studies, modest ICP elevation was consistently associated with reversible increases in sympathetic activity. In the neonatal hydrocephalus case, shunting reversed sympathetic predominance toward parasympathetic modulation. Similarly, in the HYCO cohort, shunting improved arousal and was associated with increased vagally mediated HRV indices and reduced sympathetic predominance.

Conclusion: We propose that a pressure-sensitive intracranial autonomic reflex represents a candidate interoceptive channel linking CSF hydrodynamics and brain mechanics to autonomic regulation. Within this framework, hydrocephalus emerges as a mechanobiological systems disorder in which altered CSF-brain coupling provides abnormal inputs to the CAN, potentially contributing to a low-vagal autonomic profile. Convergent observations from experimental ICP manipulation, a neonatal hydrocephalus case, and the HYCO cohort suggest that shunting may act as a form of mechanical neuromodulation, restoring autonomic balance and arousal alongside clinical improvement. ANS biomarkers may therefore provide complementary mechanobiological indicators of reversibility in hydrocephalus.

P.110 - Post-viral Postural Orthostatic Tachycardia Syndrome (POTS): A Comparison Of Two-year Outcomes In POTS Triggered By COVID-19 Vs. Other Viral Infections

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Introduction: Postural Orthostatic Tachycardia Syndrome (POTS) is highly prevalent in those with Post-Acute Sequelae of COVID-19 (PASC), however our understanding of long-term trajectory in these patients is limited. We compared 2-year outcomes between those with POTS triggered by COVID-19 (PASC-POTS) and other viral infections (OINF-POTS).
Methods:
Consecutive POTS registry participants ≥16 years receiving standardised care, consisting of lifestyle modifications and pharmacotherapy, between May-2021 and March-2024 with baseline and 2-year follow-up data were included. Patient-reported-outcome-measures to quantify autonomic symptom burden (Composite-Autonomic-Symptom-Score; COMPASS-31), fatigue (Fatigue Severity Scale; FSS-9), health-related quality-of-life (HrQoL; EQ-Utility-Score) and likelihood of generalised joint hypermobility (Hakim-5-point questionnaire≥2) were evaluated between PASC-POTS and OINF-POTS. A secondary analysis included those with symptom duration ≤5 years.

Results: A total of 90 participants were included [PASC-POTS=37; OINF-POTS=53; 81.1 vs. 86.8% female (P=0.46)]. The PASC-POTS cohort were older than the OINF-POTS group [40 (IQR 31.0-50.0) vs. 31 (24.5-37.0) years; P<0.001), with shorter symptom duration [1.0 (0.0-1.0) years vs. 5.0 (1.5-12.0) years respectively; P<0.001). At baseline, overall autonomic symptom burden (Total COMPASS-31) was similar between groups (P=0.28), but we found less fatigue in OINF-POTS (P<0.05). Joint hypermobility was similar between groups [56.8% PASC-POTS vs. 64.2% OINF-POTS (P=0.48)]. Midodrine, ivabradine and fludrocortisone were the most commonly utilised medications across the follow-up period (POTS-PASC vs. OINF-POTS: 81.1 vs. 81.1%; 16.2 vs. 15.1%; 54.1 vs. 39.6% respectively; all P>0.05). We found no differences in change in total COMPASS-31 or its subdomains (P>0.05) across follow-up. Fatigue improved more in PASC-POTS compared to OINF-POTS (P=0.03), with no difference in change in HrQoL (P=0.33). Secondary analysis with symptom duration ≤5 years (PASC-POTS; n=37; OINF-POTS; n=27) revealed no difference in results.

Conclusion: Autonomic symptom burden and HrQoL was similar between groups. Results suggest that patients present and respond to standardised care similarly regardless of viral trigger type. Future studies should focus on understanding underlying mechanisms of viral-driven POTS, and comparison of specific treatment effects.

P.111 - Thoracic Sympathectomy As A Dynamic Model Of Autonomic Remodeling: Preoperative Phenotyping And Surgical Outcome In Primary Hyperhidrosis

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Introduction: Primary hyperhidrosis is increasingly recognized as a manifestation of autonomic dysregulation characterized by excessive sympathetic activity. While endoscopic thoracic sympathectomy (ETS) is an established therapeutic intervention, patient selection remains largely symptom-based and does not routinely incorporate objective autonomic assessment. This study explores whether autonomic phenotyping using heart rate variability (HRV), serum cortisol levels, and quantitative sweat mapping can identify a distinct hyperadrenergic phenotype and help predict surgical benefit.

Methods: Thirty consecutive patients with severe primary palmar and/or axillary hyperhidrosis were prospectively enrolled. Preoperative evaluation included standardized autonomic assessment using 5-minute resting HRV analysis (time- and frequency-domain indices), morning serum cortisol measurements, and quantitative sweat mapping. Clinical severity was assessed using the Hyperhidrosis Disease Severity Scale (HDSS) and validated quality-of-life instruments. All patients underwent bilateral ETS. Postoperative follow-up included assessment of symptom relief, patient satisfaction, quality of life, compensatory sweating patterns, and changes in autonomic parameters. Associations between preoperative autonomic markers and surgical outcomes were analyzed.

Results: Preliminary findings indicate that autonomic phenotyping successfully characterizes varying degrees of sympathetic predominance within the study cohort. Patients presenting with greater preoperative autonomic imbalance demonstrated more pronounced improvements in HDSS scores and postoperative quality-of-life measures following ETS. Early postoperative assessment revealed trends toward normalization of autonomic parameters, including HRV indices and cortisol levels, suggesting a measurable shift in autonomic regulation after surgical interruption of the thoracic sympathetic chain. Ongoing analyses are quantifying the relationship between baseline autonomic phenotype and the magnitude of clinical response.

Conclusion: Thoracic sympathectomy may represent more than a localized treatment for hyperhidrosis, serving as a human model of autonomic neuromodulation and remodeling. Objective autonomic phenotyping using HRV, cortisol levels, and sweat mapping may improve patient selection and identify individuals most likely to benefit from surgical sympathetic modulation. These findings support a precision medicine approach to sympathetic surgery and provide a translational framework linking clinical thoracic surgery with contemporary autonomic neuroscience.

P.112 - Autonomic Control Of The Glymphatic "brain Drain"

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The glymphatic system is a waste clearance system unique to the brain that clears macromolecular waste through the pulsation-driven bulk flow of cerebrospinal fluid though the perivascular space. Although the mechanism driving bulk-flow of cerebrospinal fluid through the glymphatic system is understood, the systems regulating glymphatic function remain opaque. Given the apparent reliance on cerebrovascular tone, we propose that the sympathetic nervous system, which regulates vascular tone, is an important regulator of glymphatic activity. Sympathetic drive to the larger, more superficial cerebral vasculature was modulated via the cervical sympathetic trunk while the tone of deeper and smaller cerebral vasculature were targeted via the Locus Coeruleus (LC), a bilateral brainstem nucleus located in the pons. We hypothesized that increasing sympathetic drive to these vessels would impair glymphatic influx by reducing vascular pulsatility, and that glymphatic influx would improve ablation of this sympathetic drive.

In adult male Wistar rats under ketamine+medetomidine anaesthesia, glymphatic influx was assessed via intracisternal infusions of fluorescent tracers, followed by a 40-minute diffusion period.. The LC was unilaterally targeted for stimulation (n=6), ablation (n=4), or sham (n=6) procedures using a stereotactically-placed bipolar stimulation electrode. Following completion of the diffusion period, rats were euthanised with sodium pentobarbital (1mL, i.p) and the brain fixed, sectioned and imaged under fluorescent microscopy.

Comparing ipsi:contralateral fluorescence ratios revealed that pilot studies of cervical sympathetic trunk activation had no effect ($p>0.05$), while LC activation was associated with increases in fluorescence ratios (1.6 ± 0.3vs1.2 ± 0.2 au, $p<0.05$). A pilot LC ablation study (n=4) showed no effect on glymphatic function in Wistar rats (1.4 ± 0.7vs1.3 ± 0.2 au, $p=0.641$).

These results indicate that changes in vascular tone at the level of the large cerebral vessels have minimal influence over glymphatic influx. Furthermore, these experiments indicate that increased sympathetic drive to the smaller neural vessels may actually enhance glymphatic function, suggesting a more complex relationship between sympathetic activity, vascular pulsatility, and glymphatic influx than previously appreciated. Future studies will examine the effect of LC modulation on local cerebral blood flow arterial pressure and in disease models associated with chronic sympathetic overactivity such as hypertension.