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Clinical neurocardiology: defining the value of neuroscience-based cardiovascular therapeutics – 2024 update

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Conception or design of the work and drafting the work or revising it critically for important intellectual content: all authors. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Additional information

Competing interests

Olujimi Ajijola: Ownership interest in Neucures and Neufera. Stock in nFerence and Anumana. Kalyanam Shivkumar: Ownership interest in Neucures and Neufera. Stock in nFerence and Anumana.

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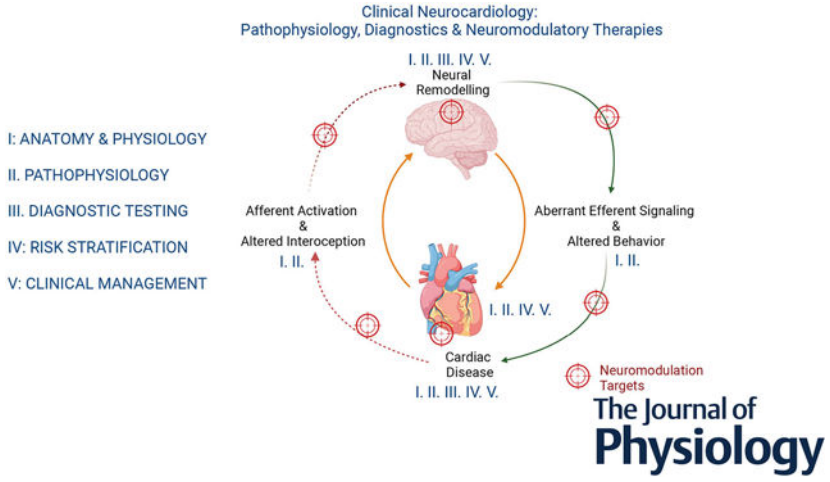
Abstract

The intricate role of the autonomic nervous system (ANS) in regulating cardiac physiology has long been recognized. Aberrant function of the ANS is central to the pathophysiology of cardiovascular diseases. It stands to reason, therefore, that neuroscience-based cardiovascular therapeutics hold great promise in the treatment of cardiovascular diseases in humans. A decade after the inaugural edition, this White Paper reviews the current state of understanding of human cardiac neuroanatomy, neurophysiology and pathophysiology in specific disease conditions, autonomic testing, risk stratification, and neuromodulatory strategies to mitigate the progression of cardiovascular diseases.

Graphical Abstract



Clinical neurocardiology: pathophysiology, diagnostics and therapeutics. Illustrated is a summary of bidirectional interactions between the heart and nervous system, with a pathophysiological lens, which captures afferent and efferent elements of the neuro-cardiac loop and their contributions to both neural and cardiac diseases.

Keywords

arrhythmias; autonomic neuroscience; cardiovascular; heart failure; neurocardiology; neurophysiology; parasympathetic; sympathetic

Introduction

The complex and vast contribution of the autonomic inputs to physiology across scales is critical to cardiovascular function. Utilizing diverse sensing mechanisms, integrating across various nexus points, and relaying reflex responses to the cardiovascular system via efferent sympathetic and parasympathetic mechanisms, and by circulating factors, the autonomic nervous system (ANS) governs cardiac homeostasis across long- and short-time scales. This fundamental and intricate control in normal states also implicates the ANS in the development and progression of cardiovascular diseases (hypertension, heart failure, arrhythmias and myocardial infarction) and cardio-respiratory diseases such as sleep apnoea.

Sympathetic hyperreflexia and parasympathetic hypotonia (mediate by attenuated central drive) are central features of several cardiac disorders. Indeed, identifiable measures of ANS function provide prognostic value, and are associated with arrhythmias and sudden death (Chugh et al., 2008; Shen & Zipes, 2014). Thus, interventions targeting pathophysiological mechanisms within the ANS remain attractive in the quest to develop novel therapeutic strategies against cardiovascular disease (Schwartz, 2014; Vaseghi & Shivkumar, 2008). This White Paper summarizes the current state of knowledge, including important updates since the 2016 paper, with a focus on: (1) anatomy and physiology, (2) pathophysiology, (3) autonomic testing, (4) risk stratification, and (5) clinical management (Table 1).

Anatomy and physiology

As function follows form, the anatomical organization of the cardiac nervous system, albeit incompletely understood, suggests that it acts as a distributive processor under the control of the central nervous system (CNS). (See Shivkumar et al. (2016) and Herring (2025) for detailed review of cardiac neuroanatomy.) Its multiple nested feedback control loops, each with different latencies of function, modulate regional cardiac indices throughout each cardiac cycle to assure adequacy of cardiac output in physiological states (Fig. 1). What is now becoming evident is the fact that such complex control depends upon the behaviour of its various neuronal elements given the fact its peripheral reflexes exert considerable influence on regional cardiac rate and force. Thorough understanding of the nerves controlling the heart is a prerequisite for therapeutic neuromodulation.

Cardiac interoception.

Understanding the complex neuroanatomy and functionality of the cardiac nervous system requires a foundational backdrop for exploring further intricacies of cardiac function and identifying how the heart communicates with the peripheral and central nervous systems. Cardiac interoception refers to the process by which the nervous system senses, interprets and integrates signals from the cardiovascular system, providing a moment-by-

moment mapping of the cardiovascular landscape that is represented at non-conscious as well as conscious levels (Cameron, 2002; Khalsa et al., 2018; Sherrington, 1961). Since the foundational descriptions of cardiac interoception, the field has witnessed significant progress in delineating the neural pathways and mechanisms underlying this vital sensory process. Contemporary studies not only build on the understanding of non-conscious mechanisms but also increasingly elucidate the role of conscious perception and its neural correlates (Berntson & Khalsa, 2021). Advances in neuroimaging and neurophysiology have enabled a more detailed mapping of cardiac interoceptive signals, which are crucial for both physiological regulation and the subjective experience of cardiovascular states. These signals are primarily transmitted through baroreceptors (Dworkin et al., 2000), chemoreceptors (O'Regan & Majcherczyk, 1982), the renin–angiotensin–aldosterone system (Re, 2004), the ANS (Janig, 1996) and the intrinsic cardiac nervous system (Rajendran et al., 2015). A nuanced appreciation has developed for how cardiovascular diseases manifest through these systems, with symptoms such as palpitations encompassing a spectrum from benign exertion to pathological arrhythmias. Furthermore, the intersection of cardiac symptoms with psychiatric comorbidities like anxiety and depression (Cohen et al., 2015) underscores the complex interplay between interoception, symptom perception and therapeutic approaches (Khalsa et al., 2014, 2021). Identifying precise neural circuits of interoception and their functional implications remains a pivotal challenge, with implications for tailored treatments in cardiovascular and neuropsychiatric conditions.

Questions and controversies

- What are the relative contributions of peripheral *versus* central reflexes in control of cardiac function in health *versus* disease.
- What is the role of non-neuronal cells (microglia, satellite, glial cells and immune cells) in autonomic control of the heart in sympathetic, parasympathetic and sensory ganglia.
- How do sex differences impact cardiac autonomic reflex function?

Advancements in measuring cardiac interoception.

Assessment methods have evolved, yet challenges remain (Khalsa & Lapidus, 2016). Traditional tasks like heartbeat counting, tapping and detection offer insights but have inherent biases and complexities, like the reliance on prior knowledge (Desmedt et al., 2018; Ring & Brener, 2018) and complicated analysis techniques. Several new tasks have also been reported, including computational modelling of interoceptive precision (Smith et al., 2020), computational modelling of metacognitive processing (Legrand et al., 2022), heart rate estimation (Larsson et al., 2021), as well as mobile assessments (Plans et al., 2021). These methods typically overlook the fluctuating intensity of cardiac sensations relevant to emotional and clinical contexts, and the difficulty in perceiving heartbeat sensation under physiological resting conditions. Methodologies introducing pharmacological perturbation have reveal individual differences in interoception. Isoproterenol infusion, for example, enhances experimental control and participant perception, ensuring comprehensive assessment across all individuals, despite the need for intravenous access (Khalsa, Rudrauf, Sandesara et al., 2009; Khalsa et al., 2016).

Modulators of cardiac interoception.

Accruing evidence indicates that interoceptive acuity declines with age (Khalsa, Rudrauf, & Tranel, 2009; Murphy et al., 2018) and higher body mass index (Kleckner et al., 2015; Rouse et al., 1988). It is also transiently enhanced during physical exertion (Koteles et al., 2020). While sex-related differences are uncertain (Prentice & Murphy, 2022), anxiety disorders notably affect interoceptive sensitivity. Panic disorder patients, for instance, respond more intensely to interoceptive challenges induced by various pharmacological agents such as caffeine (Charney et al., 1985; Zoellner & Craske, 1999), carbon dioxide (Rassovsky & Kushner, 2003), sodium lactate (Dillon et al., 1987), yohimbine (Gurguis et al., 1997), cholecystokinin (Schunck et al., 2006) or isoproterenol (Pohl et al., 1988). Generalized anxiety disorder patients similarly show heightened sensitivity to isoproterenol-induced perturbation, as evidenced by elevated heart rate, heightened cardiac sensation and increased anxiety (Teed et al., 2022). These data suggest the inherent threshold for cardiac sensation varies from person to person, but might be modulated by demographic characteristics, acute physiological state and/or psychiatric illness.

Cardiac interoception in cardiovascular disorders.

Cardiac interoception persists even with mechanical heart support (Couto et al., 2013) or after heart transplantation (Barsky et al., 1998; Salamone et al., 2020), indicating alternative, non-viscerosensory pathways for heart perception (Khalsa, Rudrauf, Feinstein et al., 2009; Knapp-Kline et al., 2021). Post-myocardial infarction (Jones et al., 1985), hypertension (Koroboki et al., 2010; O'Brien et al., 1998) or chest pain diagnosis (Schroeder et al., 2015) does not generally alter resting cardiac interoception. Patients with atrial fibrillation (AF) may misinterpret heart rhythms (Flaker et al., 2005; Hindricks et al., 2005), with abnormal electroencephalographic markers (Kumral et al., 2022) suggesting disrupted heart–brain communication (Khalsa & Verdonk, 2022). Anxiety-related overestimation of AF episodes (Garimella et al., 2015) and impaired quality of life (Sadlonova et al., 2024) point to a potential target for improving patient outcomes (Minjie et al., 2023).

Predictive coding in neurovisceral integration.

Human neuroimaging studies of cardiovascular sensation consistently support a role for the insular cortex (Hassanpour et al., 2018), but they also identify a broader network that includes the somatosensory cortex and prefrontal regions (Critchley et al., 2004; Schulz, 2016; Teed et al., 2022), highlighting the brain's predictive role in interoception. Constructivist perspectives also suggest that interoceptive perceptions are unconsciously influenced by (or may even directly reflect) the brain's predictions about the state of the body (Barrett & Simmons, 2015; Seth & Friston, 2016). Discrepancies between predicted and actual bodily states – 'interoceptive prediction errors' – prompt compensatory adjustments in order to restore balance (Paulus & Stein, 2010) (Fig. 2A). The brain may reduce interoceptive prediction error by attenuating the processing of incoming sensory input, by triggering changes in the body that resemble the expected (i.e. predicted) input, or by altering perceptual inferences about bodily states. These observations have informed an updated model of neurovisceral integration (Smith et al., 2017), which postulates that the hierarchical organization of neural circuits involved in autonomic regulation spans from the

cortical level (involving networks for higher cognition and emotional processing) through the brainstem and peripheral cardiovascular reflex arcs down to the heart (Fig. 2B). Nested hierarchies within each level of the central autonomic network include sub-levels of error-related feedback regulation and control, allowing for nuanced and context-specific responses to internal and external stimuli. This revised model emphasizes the nested, multi-level regulation occurring within the central autonomic network (Beissner et al., 2013; Ferraro et al., 2022), which facilitates the integration of other types of visceral signals, leads to coordinated autonomic responses and allows the system to modulate its responses based on perceived environmental demands and internal states. This adaptability is a marker of health, with greater flexibility in autonomic responses being associated with better cardiovascular and mental health outcomes. The dynamic and integrated nature of these heart–brain interactions implies that interventions aimed at improving autonomic flexibility, such as biofeedback or stress management techniques, could have beneficial effects on both neurological and cardiac health.

Questions and controversies

- How can we delineate the neural pathways and mechanisms of cardiac interoception at non-conscious and conscious levels, and what implications would this have for understanding the integration of cardiac signals?
- Which validated methods for measuring cardiac interoception demonstrate the best reliability and practicality for clinical application, and how could they improve patient assessment?
- In what ways does the brain’s interoceptive predictive coding process align with the physiological signals and subjective experiences of cardiac interoception, and how could this inform treatments for neurocardiac disorders?
- Can any human technologies disentangle the relative contributions of afferent and efferent pathways in the brain-body feedback loop, and how could this knowledge influence therapeutic interventions?

Pathophysiology

Autonomical control of the sinoatrial node in health disease and ageing.

Maladaptive signalling between the heart and its neural hierarchy is central to the pathophysiology of cardiovascular diseases. Sympathetic hypo- and hyper-reflexia, as well as hypo- and hyper-vagotonia are known to contribute to cardiovascular diseases. Mechanisms by which the aforementioned neural processes occur are covered here.

‘Normal’ sinoatrial node ageing.

The integration of numerous mechanisms intrinsic to cardiothoracic tissue and sinoatrial node (SAN) pacemaker cells, and modulation of these mechanisms by the ANS surveillance adjust the times at which the next heartbeat occurs (aka heart rate variability, HRV) to optimize cardiac output to the body’s acute requirements (Armour, 2008; Rosenberg et al., 2020; Weiser-Bitoun et al., 2021). As age increases, one or more of the components of

physiological coupling within the neuroautonomic, sinus node and atrial regulatory network begins to deteriorate. ‘Normal’ SAN ageing includes an increased heart interval variability at rest (Choi et al., 2022; Costa et al., 2017a; Jose & Collison, 1970), increased numbers of SAN impulse pauses, increased SAN recovery time and a reduction in the maximal rate at which the heart can beat (Fleg et al., 2005). Findings in animal models recapitulate many aspects of HRV described in humans (Dorey et al., 2021; Moen et al., 2022; Moghtadaei et al., 2024; Peters et al., 2020; Segal et al., 2023; Weiser-Bitoun et al., 2023; Whitehead et al., 2014; Yaniv et al., 2016). In response to ANS input, HRV occurs gradually over several beats, whereas HRV arising from mechanisms intrinsic to the SAN occur abruptly (Lensen et al., 2020; Weiser-Bitoun et al., 2021). Selective electronic filtering of ANS input revealed that in younger persons both intrinsic SAN mechanisms and ANS input contribute to both long- and short-range HRV in electrocardiogram (ECG) RR interval time series; but in older persons, while intrinsic SAN mechanisms contribute to both short- and long-term HRV, the ANS contributes only to short-term HRV (Weiser-Bitoun et al., 2023). A seminal study recoding ECGs at 3-month intervals throughout the adult life of mice discovered that a marked reduction of the percentage high frequency power, accompanied by an increase in percentage very low frequency power during autonomic blockade began to emerge at about 20 months of age (~60% of mouse lifespan), and that beyond that age the rates at which high frequency become further reduced and very low frequency increased in individual mice markedly accelerated (Moen et al., 2022). ECG time series fragmentation analyses indicate that fluctuations in ECG RR intervals that compete with or even exceed the shortest-term modulatory responsiveness of the ANS emerge as age increases, leading to increased RR interval fragmentation (Costa et al., 2017a, 2017b; Costa & Goldberger, 2019; Domitrovich & Stein, 2002; Lensen et al., 2020; Stein et al., 2002). In longitudinal multi-scale multi-fractal detrended fluctuation analysis, RR interval fractals that diverged from expected boundaries and that were substantially larger during autonomic blockade, indicating instability of the heart rate control system due in large part to a decline in intrinsic SAN function, began to emerge in individual mice at about 3 months prior to the end of their natural lifespan (Moghtadaei et al., 2024). In summary, because it ultimately progresses to sick sinus syndrome, SAN failure and AF, ‘normal SAN ageing’ is the major shareholder in *clinical* SAN disease (Lakatta & Levy, 2003; Lakatta, 2015).

Mechanisms of normal sinoatrial node ageing.

In addition to age-associated increase in SAN fibrosis and a reduction in the number of SAN pacemaker cells (Liu et al., 2014; López-Otín et al., 2013), the coupled-clock system (Fig. 3) that drives spontaneous action potential (AP) firings in SAN pacemaker cells (Bogdanov et al., 2001; Lakatta et al., 2010; Lyashkov et al., 2018; Tsutsui et al., 2018; Tagirova Sirenko et al., 2021) deteriorates as age advances (López-Otín et al., 2013; Liu et al., 2014; Peters et al., 2020). A reduced Ca^{2+} influx rate during AP cycles in aged SAN cells and sluggish sarcoplasmic reticulum (SR) Ca^{2+} cycling, linked to a reduced rate of decay of the increase cytosolic Ca^{2+} generated by the prior AP, both contribute to a reduction in Ca^{2+} loading within the SR (Liu et al., 2014). Spontaneous, stochastic local Ca^{2+} oscillations (LCO) emerge from the SR at a later time following the prior AP, and age-associated changes in LCO characteristics prolong the self-ordering process of LCOs required to create ensemble Ca^{2+} signals required to ignite AP firing within the ‘membrane clock’ (Liu et al., 2014), in

which numerous players change with ageing (Huang et al., 2007; Jones et al., 2007; Peters et al., 2020). This results in prolongation of intervals between APs, and to increased variability of AP intervals, that is, in ‘AP cycle fragmentation’ in SAN cells as age increases (Moen et al., 2022).

An inability of autonomic input to fully compensate for the age-associated increase of fragmentation of AP firing intervals *in vivo* (Moen et al., 2022; Yaniv et al., 2016) is linked to reduced sensitivity to cAMP in *ex vivo* SAN tissue of old mice (Kirschner Peretz et al., 2023; Segal et al., 2023), and in SAN pacemaker cells reduced cAMP-dependent phosphorylation of clock proteins (Florea et al., 2012; Liu et al., 2014), leading to reduced synchronization of clock protein functions (Shivkumar et al., 2016; Tagirova Sirenko et al., 2021; Yang et al., 2021). Functional alterations in SAN tissue and pacemaker cells are rooted in age-associated changes in transcription, translation and post-translational modifications of SAN proteins, which create desynchronization of molecular interactions (Lakatta, 2004), leading to changes in stoichiometry, and in particular, to reduced kinetics of molecular signalling that is crucial to SAN and SAN pacemaker cell clock functions and their coupling (Lakatta, 2015; Monfredi & Lakatta, 2019). As a result, as aged SAN cells fail to appropriately generate and transmit signals, the molecular targets of these signals fail to appropriately sense and respond to signals that regulate the timing at which the next SAN impulse occurs. Future studies are required to determine whether ageing also compromises the phase alignment and synchronization of spontaneous APs generation *among* pacemaker cells embedded within SAN tissue (Fig. 4) (Bychkov et al., 2020, 2022; Donald & Lakatta, 2023).

Intramyocardial neural–myocyte interface remodelling

Myocardial infarction/ischaemic cardiomyopathy. Myocardial infarction (MI) damages the axons and causes cardiac sympathectomy in non-infarcted myocardium (Barber et al., 1983). The axonal damage is followed by increased myocardial neurotrophic factor gene expression (Oh et al., 2004). These neurotrophic factors could be transported through retrograde axonal transport to the stellate ganglion (Zhou et al., 2004) to cause neural remodelling and increased stellate ganglion nerve activity (Han et al., 2012). The canine model of MI is usually not followed by a high incidence of cardiac arrhythmias. However, if there is additional electrophysiological and neural remodelling caused by the atrioventricular (AV) block and nerve growth factor (NGF) infusion into the stellate ganglion, the MI dogs would develop a high incidence of ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (Cao, Chen et al., 2000). Extensive cardiac nerve sprouting and sympathetic hyperinnervation can be detected in those models. In patients with VT who underwent ambulatory skin sympathetic nerve activity (SKNA) recordings, the spontaneous VT episodes are typically preceded by bursts of SKNA (Kabir et al., 2017; Kusayama et al., 2019). Acute coronary syndrome is associated with elevated average SKNA, and the magnitude of SKNA elevation is associated with the occurrence of ventricular arrhythmias (Huang et al., 2022). If the stellate ganglion nerve activity is a trigger of VT and VF, it follows that stellate ganglion resection might be curative for cardiac arrhythmia. Stellate ganglion resection has been used successfully to manage patients with inherited arrhythmia syndromes (Moss & McDonald, 1971; Schwartz et al., 2004; Wilde et al., 2008). Stellate

ganglion block has also been used in managing electrical storms in patients with MI or other organic heart diseases (Meng et al., 2017). Because the skin sympathetic nerves of the cervical and thoracic regions came from the stellate ganglion (Taniguchi et al., 1994), high frequency stimulation of the skin sympathetic nerves in the thorax may remodel the stellate ganglion (Yuan et al., 2018). In dogs with MI, subcutaneous nerve stimulation reduces the stellate ganglion nerve activity and suppresses cardiac nerve sprouting (Yuan et al., 2020). Low level vagal nerve stimulation and renal denervation are also promising methods to remodel the stellate ganglion without surgical ablation (Tsai et al., 2023; Yuan et al., 2020; Zhang et al., 2018). Whether or not these methods prevent post-MI cardiac arrhythmias and sudden death remains unknown. Prospective randomized clinical trials are needed to determine the therapeutic efficacy of various neuromodulation procedures.

Heart failure (non-ischaemic). Heart failure (HF) can be associated with both ischaemic and non-ischaemic cardiomyopathy. Similar to that found in the canine stellate ganglion after MI (Han et al., 2012), human cardiomyopathy is also associated neuronal hypertrophy within left stellate ganglia (Ajijola, Wisco et al., 2012). However, there is no evidence of increased nerve sprouting in the stellate ganglion. Patients with HF have increased sympathetic nerve activity (SNA), increased noradrenaline spillover from the heart, and increased plasma noradrenaline levels (Meredith et al., 1993). Increased muscle SNA and plasma noradrenaline concentrations are both important prognostic indicators for HF prognosis (Barretto et al., 2009; Cohn et al., 1984). The increased noradrenaline levels may play a role in the development of cardiac noradrenergic nerve abnormalities in heart failure (Himura et al., 1993). These abnormalities include the reductions of catecholaminergic histofluorescence and tyrosine hydroxylase immunostaining profiles. These data indicate that while HF is associated with elevated systemic noradrenaline levels and muscle SNA, the sympathetic innervation in the myocardium is reduced. The latter counterintuitive finding was investigated in a mouse model of dilated cardiomyopathy (DCM) (Dajani et al., 2023). The authors found that DCM models invariably exhibited transmural (epicardial to endocardial) gradients, with the endocardium being devoid of sympathetic nerve fibres versus controls. They concluded that heterogeneous innervation gradients in DCM promoted arrhythmogenesis. The heterogeneous innervation is also found in human patients with MI and ventricular arrhythmias (Cao, Fishbein et al., 2000). It is possible that during sympathetic activation, the heterogeneous innervation worsened the electrophysiological heterogeneity to induce arrhythmia. The relationship between SNA and cardiac arrhythmia has been investigated in a canine model of pacing-induced HF (Ogawa et al., 2007). In that study, the authors induced HF in dogs by rapid ventricular pacing. The dogs with HF had significantly increased both the stellate ganglion and vagal nerve activity, but only the former manifested a circadian variation pattern. Simultaneous sympathovagal discharges are associated with long episodes of paroxysmal atrial tachycardia. Cryoablation of bilateral stellate and T2–T4 thoracic ganglia significantly reduced paroxysmal atrial tachycardia and prolonged sinus pause episodes induced by sympathetic discharges in dogs with pacing-induced HF (Ogawa et al., 2009). Consistent with the canine studies, a recent clinical trial showed stellate ganglion block is effective in treating refractory electrical storm in patients with HF (Savastano et al., 2024). More studies will be needed to determine the efficacy and risks of neuromodulation in the management of HF and cardiac arrhythmias.

ANS and atrial fibrillation.

AF is the most common cardiac arrhythmia associated with significant morbidity and mortality. The aetiology of AF is multifactorial, including atrial fibrosis, atrial stretch/dilatation and inflammation. A landmark study (Haissaguerre et al., 1998) established the importance of the pulmonary veins (PV) in the generation of AF. PVs not only contain cardiac-type myocytes, but are also highly innervated (Kusayama et al., 2021). ANS activation has been shown to induce atrial tachyarrhythmias such as AF. Acetylcholine shortens the atrial/PV activation potential duration and refractory period while noradrenaline increases intracellular Ca^{2+} transients. Parasympathetic and sympathetic co-activation operates synergistically to enhance triggered activity and promote re-entry (Patterson et al., 2006). In ambulatory dogs, initiation of AF was invariably preceded by sequential or simultaneous activation of both the parasympathetic and sympathetic nervous systems (Choi et al., 2010). Clinical studies also corroborate the critical role of ANS AF genesis by showing that activation of both components of the ANS preceded AF initiation (Bettoni & Zimmermann, 2002; Lombardi et al., 2004). Dysregulation of the ANS, evidence by reduced HRV, has been shown to increase the risk of AF (Agarwal et al., 2017). Notably, among the CHA_2DS_2-VASc score, ageing, hypertension and diabetes also strongly correlate with dysregulation of ANS.

PV isolation has evolved to be the cornerstone of AF ablation. The standard lesion sets of PV isolation also transect at least three major atrial ganglionated plexi (GP), raising the question of whether ANS denervation may contribute to the success of AF ablation (Po et al., 2009). PVI + GP ablation has been shown to confer a higher success than PVI alone in patients with paroxysmal AF (Katritsis et al., 2013) but not in patients with more advanced stage of AF (Driessen et al., 2016), suggesting that ANS may be more important in an earlier stage of AF. The ERADICATE-AF trial randomized patients with paroxysmal AF with hypertension to PVI *versus* PVI + renal denervation and demonstrated PVI + renal denervation was superior to PVI at 12 months (Steinberg et al., 2020).

Premature ventricular complex-induced neural remodelling.

Premature ventricular complexes (PVC) have acute intrinsic and extrinsic effects on the heart. Intrinsically, PVCs cause dyssynchronous ventricular contraction, post-extra-systolic potentiation, AV dyssynchrony and intermittent tachycardia (Gunda et al., 2019; Huizar et al., 2019; Kowlgi et al., 2022; Lee et al., 2012; Shoureshi et al., 2023; Walters et al., 2018). Extrinsically, PVCs are a unique and potent stressor of the cardiac ANS (CANS) and perturb nerve activity across multiple levels of the neural hierarchy, including triggering increased firing of intrinsic cardiac ganglia (Hamon et al., 2017), extrinsic afferent ganglia (Salavatian et al., 2019) and efferent cardiac sympathetic nerves (Shoureshi et al., 2023). The effects of PVCs on cardiac parasympathetic activity are variable and can either increase or decrease parasympathetic activity depending on the activity state in which it is measured (Lombardi et al., 1989; Tan et al., 2020). The overall acute effect of PVCs on the CANS, therefore, is to trigger an immediate net sympathetic excess. This change serves to assist in short term cardiac adaptation against the contractile, rhythmic and haemodynamic perturbations caused by PVCs (Lombardi et al., 1989; Tan et al., 2020). However, chronic exposure to frequent PVCs causes remodelling of both the heart (Huizar et al., 2019) and the CANS

(Tan et al., 2020), resulting in dysfunction of both. Combined cardio-neural dysfunction might lead to pro-arrhythmia, maladaptive responses to physiological stress, exacerbation of heart failure (HF) and promotion of further adverse cardiac remodelling (Huizar et al., 2019; Lee et al., 2012). To further elucidate the complex inter-relationship between cardiac and autonomic remodelling caused by PVC, it is important to first note that the PVC trigger and the immediate sympathetic firing it causes occur upstream to the onset of any cardiac or neural remodelling, and therefore it is reasonable to hypothesize that autonomic remodelling might be important pathophysiological contributor to cardiac remodelling. One can conclude that autonomic remodelling caused by chronic PVC exposure further exacerbates the acute sympathetic overload triggered immediately by exposure to PVCs.

Combined cardio-neural remodelling in PVC-CM might contribute to pro-arrhythmia, worsening of HF and increased cardiac mortality (Huizar et al., 2019). In a *post hoc* analysis of over 1000 patients from the Cardiovascular Health Study, patients with frequent PVCs of at least 0.7% burden on a 24-h Holter monitor experienced a 31% increase in cardiac mortality and 48% increase in incident heart failure (Dukes et al., 2015). Noda et al. (2005) demonstrated that in patients with frequent PVCs, the PVCs might trigger malignant ventricular arrhythmias, suggesting that PVCs might provide a trigger for VT/VF in the setting of an abnormal myocardial and/or neural substrate. Simultaneous cardio-neural telemetry in canines with PVC-CM demonstrates increased incidence of spontaneous atrial and ventricular arrhythmias (Tan et al., 2020). These arrhythmias increased in burden after development of PVC-CM and sympathetic remodelling, suggesting the synergistic effects of cardio-neural remodelling. However, they persisted at higher burden after the resolution of left ventricular (LV) dysfunction, but in the setting of persistent sympathetic remodelling (Tan et al., 2020). In addition, the arrhythmias are also temporally preceded by increased sympathetic firing (Tan et al., 2020). These data indicate that autonomic remodelling is both a trigger and a substrate for arrhythmias. Isolated LV myocytes from PVC-CM hearts demonstrated heterogeneously prolonged action potential duration correlating with heterogeneous downregulation of repolarizing potassium currents such as transient outward and inward rectifier currents (Wang, Eltit et al., 2014). Thus, cellular cardiac electrical remodelling interacts with neural remodelling to promote ventricular arrhythmias.

In addition to pro-arrhythmia, autonomic dysfunction also manifests as a maladaptive response to physiological challenge such as exercise. Shoureshi et al. (2023) performed exercise challenge in canines with PVC-CM, both in sinus rhythm (SR) and in the presence of PVCs (Tan et al., 2023). This approach highlights a unique aspect of an arrhythmia-induced CM such as PVC-CM in that the arrhythmia (PVCs) is not only the cause of remodelling but acts as a constant and dynamic stressor that continually challenges a neurally remodelled heart. The results reveal that despite apparent sympathetic excess at rest, the degree of exercise-induced sympathetic augmentation is paradoxically diminished in PVC-CM, particularly in the presence of PVCs. This is consistent with loss of sympathetic functional reserve (Tan et al., 2023). In terms of the PVC-remodelled parasympathetic nervous system, although there is no increase in parasympathetic activity at rest over baseline, parasympathetic activity with exercise is augmented in PVC-CM. This augmentation is most apparent in presence of PVCs (Tan et al., 2023). During exercise recovery, the reverse was observed, in that parasympathetic activity and heart rate

recovery are both impaired. Impaired heart rate recovery after exercise has been associated with increased cardiac mortality (Cole et al., 2000). Thus, autonomic remodelling and dysfunction might have adverse prognostic implications. In summary, both sympathetic and parasympathetic dysfunction are present in a PVC-remodelled CANS. This dysfunction might contribute to a maladaptive cardiac response to exercise in patients with PVC-CM and be an important target for neuromodulation therapies.

To determine the molecular mechanisms of autonomic dysfunction, our group at Virginia Commonwealth University (unpublished observations) performed extensive molecular survey of sympathetic, parasympathetic and neurotrophic proteins throughout the CANS in canines with PVC-CM. The results demonstrate downregulation of neurotrophic markers in the intrinsic (LV myocardium) but not in the extrinsic CANS, including reduced NGF, a critical neurotrophic factor for peripheral autonomic nerves, and GAP 43, a marker of growing nerve cones. These results may seem counterintuitive at first, given the presence of widespread sympathetic hyperinnervation that typically needs to be supported by neurotrophic precursors such as NGF and GAP 43. However, it suggests that frequent PVCs and the sympathetic overload it triggers, is the primary cause of CANS remodelling and the heart responds in adaption to this sympathetic overload by neurotrophic downregulation. Secondly, neurotrophic downregulation provides a mechanistic explanation for autonomic dysfunction since NGF is critical for the survival, differentiation and functional cross talk between sympathetic and parasympathetic nerves.

Finally, whether neural remodelling contributes to pathogenesis of PVC-CM remains uncertain. Future approaches to answer this question would entail utilizing a therapeutic denervation approach to determine whether protection from chronic sympathetic overload caused by PVCs is ultimately cardioprotective or not. Blocking of specific cardiac afferent channels (TRPV1) which mitigated cardio-neural reflexes that trigger sympathetic overload in an animal model demonstrated some mitigation of the early stages of PVC-CM (Hori et al., 2021), as did left cardiac sympathetic denervation, which was cardioprotective of PVC-CM (unpublished data). Future studies are needed to confirm these preliminary findings. Establishing the mechanistic link between autonomic remodelling and PVC-CM pathogenesis could pave the way to novel neuromodulation therapies that target and mitigate autonomic remodelling as an alternative cardioprotective therapy other than PVC suppression.

Extra-cardiac neuronal remodelling and cardiac injury.

Clinical data regarding extracardiac neuronal remodelling in patients with cardiomyopathy (CMP) are abundant. In 2008, Docimo et al. (2008) reported an increased number of neuronal cell bodies within the left stellate ganglion (LSG) of 32 deceased suffering cardiopulmonary disease, compared to dead from other causes. The same group subsequently reported (Wood et al., 2010) a borderline correlation between the amount of fibrosis within the interventricular septum and the number of neuronal cell bodies in the LSG. Since stellate ganglion (SG) neurons are post-mitotic cells, a satisfactory explanation for these preliminary and yet unconfirmed findings is still lacking. Ajijola, Wisco et al. (2012) demonstrated a significant neuronal enlargement within the LSG

of CMP patients undergoing left cardiac sympathetic denervation (LCSD) for refractory ventricular arrhythmias (VAs, $n = 31$), compared to cadaveric controls ($n = 3$). Patients without myocardial scar ($n = 7$) had even larger neurons compared to patients with scar ($n = 24$). Intraganglionic fibrosis, synaptic density and nerve sprouting were not different across groups. In a subsequent study (Ajijola et al., 2017), the same group performed a more advanced analysis (Fig. 5) to compare the SG of CMP patients receiving cardiac sympathetic denervation (CSD; $n = 16$) to those of age-matched organ donors ($n = 8$). Specific inflammatory changes were detected in CMP patients, including larger lipofuscin deposits, extensive mitochondrial degeneration and the presence of $CD3^+$ T cell infiltration and of activated macrophages. Notably, macrophage activation in the SG was recently associated with VAs in a rat model of acute lung injury (Hong et al., 2021), while macrophage depletion in the SG was proved to significantly reduce sympathetic overactivation and VAs in a rat model of congestive HF, confirming the importance of these findings (Zhang et al., 2021). Signs of a dysfunctional sympathetic activity were also detected, while a preserved preganglionic cholinergic innervation was noticed with no significant trans-differentiation. Finally, glial cells within the SG had a preserved distribution and relationship to neurons but were significantly more activated. The striking observation of glial cell activation, first in this setting, well fits with the existing bidirectional interactions between glial cells and the surrounding neurons and preganglionic nerve terminals and represents an area of intense research, with animal transcriptomic profiling studies at the single cell level confirming an extreme dynamicity of satellite glial cells within the SG (van Weperen et al., 2021). Accordingly, a pronounced glial cell activation within the SG was subsequently demonstrated in a rat model of ischaemic HF (Tu et al., 2022). Also, it was suggested (Feldman-Goriachnik & Hanani, 2019) that satellite glial cells within the sympathetic ganglia, as opposed to those within sensory ganglia, may be specifically activated by sympathetic nerve damage, further supporting the findings of Ajijola et al. (2017).

Neural biomarkers of cardiac remodelling: neuropeptide Y and galanin.

The first report about increased neuropeptide Y (NPY) peripheral plasmatic levels in patients with acute myocardial ischaemia (Ullman et al., 1990) and heart failure (Maisel et al., 1989) dates to the late 1980s–early 1990s. In 2013 (Cuculi et al., 2013), NPY peripheral levels, assessed both before and after percutaneous revascularization in 64 patients with acute ST elevation myocardial infarction (STEMI), were directly related with blood pressure and heart rate at presentation and inversely related with coronary flow, ST resolution and coronary flow reserve, suggesting a double role for NPY, both as a marker of myocardial reperfusion (the higher the NPY, the lower the reperfusion) and as a therapeutic target to improve it. These preliminary data were recently confirmed by the same group first in a smaller study ($n = 45$) (Herring et al., 2019), and then in a larger study (Gibbs et al., 2022) including 164 STEMI patients undergoing a detailed evaluation of microvascular function with angiographic and cardiovascular magnetic resonance indexes. NPY levels in the peripheral venous blood and in the coronary sinus were highly correlated ($r = 0.92$; $P < 0.001$) and both associated with microvascular function and infarct size. In the second study, peripheral NPY levels were also independent predictors of HF or mortality during follow-up. Finally, in patients with anterior STEMI undergoing primary percutaneous revascularization (Kalla et al., 2020), higher NPY levels were associated with peri-periprocedural VAs.

A recent study (Ajijola et al., 2020) in the setting of chronic congestive HF included 105 patients (mean LV ejection fraction (LVEF) 26 ± 7%) undergoing coronary sinus blood sampling during cardiac resynchronization therapy implantation. NPY levels ≥130 pg/ml were associated with an increased risk of the composite endpoint of death, heart transplantation or LV assist device implantation, even after adjusting for age, renal function and LVEF. The latest and largest study (McDowell et al., 2024) included a total of 833 outpatients with chronic HF of all types (mean LVEF 26 ± 7%, including 30% with preserved LVEF), undergoing peripheral venous NPY sampling. NPY levels ≥29 pg/ml were associated with some baseline characteristics, most of them suggesting more advanced HF (male sex, higher brain natriuretic peptide (BNP) levels, lower estimated glomerular filtration rate and diuretic usage) and with a greater risk of cardiovascular and all-cause death, while no association with HF hospitalization was detected. Overall, the strength of NPY as a biomarker in HF appears to be related to its association with cardiovascular death above and beyond natriuretic peptide. From a practical standpoint, the main issue with NPY level assessment is that it requires that samples are processed immediately by centrifugation and aliquoted and stored at −80°C until assay.

Clinical data for galanin are very limited so far. A recent study including 57 patients with HF with reduced LVEF (28.9 ± 6.6%) (Ozkaramanli Gur et al., 2017) and 30 controls showed that, unlike pro-BNP, copeptin and NPY, galanin was not elevated in chronic HF patients nor correlated with echocardiographic parameters of HF severity. Another study demonstrated that galanin, but not with NPY, could promote *in vitro* an anti-thrombotic phenotype on endocardial endothelial cells from HF patients (Tyrrell et al., 2017).

Higher centres.

Cardiovascular diseases may originate from aberrations in CNS control of peripheral sympathetic and/or parasympathetic control of the heart. Specifically, neural remodelling present in obstructive sleep apnoea (OSA) and HF is recognized to occur with significant consequences that include enhanced and unvarying sympathetic discharge, accompanied by reduced parasympathetic tone. This clinical scenario results in hypertension, and phase-shifted or unresponsive blood pressure responses to autonomic, ventilatory, or motor challenges (see Shivkumar et al., 2016 for details).

The evidence suggests that the injuries introduced by OSA and HF modify cardiovascular action, as demonstrated by flawed neural responses to transient challenges, distorted cardiovascular responses to those challenges, and altered baseline cardiovascular activity. However, the injury is not all-or-none; the data suggest that the injury is progressive, leaving the possibility that early intervention can halt or reverse the damage. Both OSA and HF are accompanied by profuse sweating and other aspects of high fluid loss, leaving the possibility of high nutrient loss that can be corrected. Interventions to support the blood–brain barrier and acute damage may provide a mechanism to prevent such tissue injury.

Autonomic remodelling and hypertension.

Whilst there has always been much debate about the causative nature of autonomic imbalance and the development of hypertension (HTN), there is increasing evidence that

autonomic changes precede the onset of HTN in susceptible individuals. For example, exaggerated blood pressure (BP) responses occur during exercise testing in pre-HTN individuals (Matthews et al., 1998). More recently, Jung et al. (2018) looked at heart rate recovery after peak exercise in 556 participants. In the 279 with pre-HTN, heart rate recovery was significantly lower. In addition, individuals in the pre-HTN group demonstrated more metabolic disturbance and subclinical organ damage. Direct evidence for sympathetic overdrive comes from microneurography studies that demonstrate that muscle SNA (MSNA) correlates to diastolic BP at baseline (Hering et al., 2016) in studies that show impaired arterial baroreflex sensitivity (Fonkoue & Park, 2018). There is also evidence for lowered vagal activity measured using HRV in the offspring of hypertensive patients (Piccirillo et al., 2000).

In established HTN, Wallin's seminal work in the 1970s, corroborated by Esler almost 30 years later, established a direct link between elevated MSNA and HTN (Esler, 2000; Wallin et al., 1973). Esler and colleagues also developed the noradrenaline spillover technique that not only measures whole body SNA (Esler et al., 1979) but was also used to demonstrate that cardiac and renal spillover are elevated in HTN and that SNA is elevated differentially in different stages of HTN (Esler et al., 1989; Grassi et al., 1998). More recently, there has been an interest in sex differences with evidence that sympathetic remodelling varies between men and women, that sex steroid hormones may affect the vasoconstrictor response to underlying levels of SNA, and that HTN risk increases in post-menopausal women because a β-adrenergic vasodilatory response to noradrenaline is replaced by an α-vasoconstrictor response (Briant et al., 2016; Hart et al., 2011).There now exist a number of device-based therapies that directly target sympathetic activity such as renal sympathetic denervation (Symplicity et al., 2010), carotid body stimulation (Heusser et al., 2010) and even deep brain stimulation (Patel, Javed et al., 2011; Pereira et al., 2010).

One potential mechanism of HTN is known as the 'selfish brain hypothesis', proposed by Dickinson in 1991 (Candelario-Jalil, 1991). The theory posits that the brain aims to preserve its cerebral blood flow to stay perfused and should increase systemic BP if cerebral artery flow is diminished (e.g. due to atherosclerosis). This theory was revisited by Paton in 2009, specifically in relation to brainstem hypoperfusion (Paton et al., 2009). There is now increasing clinical evidence for this theory including cardiovascular magnetic resonance imaging (MRI) showing correlation of vascular resistance in the posterior circulation to HTN (Rodrigues et al., 2015), as well as anatomical variation in the posterior circulation and vertebral arteries (Manghat et al., 2022). Further evidence for direct sympathetic excitation comes from studies looking at lateral medullary compression by vascular loops, although this probably represents a small subset of HTN patients and is a primary rather than a secondary phenomenon (Jannetta & Gendell, 1979). Other theories include sympathetic overdrive (excessive adrenergic response to environmental factors) (Julius et al., 1982), chemoreceptor stimulation by ischaemic hypoxia (Trzebski, 1992), and involvement of the metabolic and humoral systems (Chakraborty et al., 2020).

Whist the sympathetic system has been widely investigated with respect to HTN, there is good evidence that changes in the parasympathetic nervous system also occur. For example, Langewitz et al. (1994) compared normotensive to borderline and hypertensive

men by looking at HRV and respiratory-linked fluctuations and found that activity was significantly reduced in the vagal band although sympathetic changes were greater. In newly diagnosed HTN patients, other authors have found reduced parasympathetic tone (Goit & Ansari, 2016). One potential mechanism for parasympathetically mediated HTN would be through the renin–angiotensin–aldosterone system (Shanks & Ramchandra, 2021). For example, angiotensin II tonically inhibits cardiac vagal tone – both peripherally, via preor post-ganglionic neurones (Rechtman & Majewski, 1993), and centrally, probably via the nucleus tractus solitarius (NTS). In addition, there is clinical evidence for a progressive impairment of cardiac vagal modulation in HTN (Mancia & Grassi, 2014).

Other factors that may be relevant for baseline autonomic activity and therefore contribute to changes seen in HTN include genetic, racial and extrinsic (environmental) factors and concomitant disease such as diabetes or metabolic syndrome. Whilst genetics is likely to play a very small part (<1%) in most studies, racial difference almost certainly do play a part. One study found that HRV is consistently higher in African-American subjects than European Americans, which correlated to higher levels of HTN (Hill & Thayer, 2019). Regarding psychosocial stress, a recent meta-analysis demonstrated that it is associated with an increased risk of hypertension, and hypertensive patients have a higher incidence of psychosocial stress than normotensives (Liu et al., 2017). However, whether this is causative is unknown.

Sympathetic neural mechanisms in normal and disrupted sleep.

Normal sleep comprises a complex, heterogenous and structured series of brain state changes, which we define using the polysomnogram (a montage of measures of the electroencephalogram (EEG), the electrooculogram (EOG) and the electromyogram (EMG)) complemented by measures of breathing, oxygen saturation and the EMG. Using the first three sets of sensors, we currently classify sleep (AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications) as N1 (light sleep), N2 and N3 (deep sleep) stages of non-REM sleep, and REM sleep, the sleep stage when dreams are most likely to occur. The transition from wakefulness to light to deep sleep is accompanied by progressive decreases in central sympathetic outflow as measured by microneurography, together with slowing of heart rate and reduction in BP, so that sympathetic activity, heart rate and BP are at their lowest during N3 or deep sleep, when the EEG shows high amplitude slow waves. During REM sleep, when the EEG shows low amplitude high frequency brain waves, rapid eye movements on the EOG, and loss of muscle tone evident on the EMG, there are abrupt and striking increases in sympathetic (and parasympathetic) activity, with rapid fluctuations in heart rate and in BP. The profound changes in autonomic balance in REM can result in striking REM-associated bradyarrhythmias that may range from Wenckebach second degree heart block to periods of asystole lasting well over 10–15 s even in healthy young subjects (Guilleminault et al., 1984). Increases in heart rate and BP during REM may also trigger episodes of nocturnal ischaemia, evidenced by REM-related changes in the ST segment of the ECG (Nowlin et al., 1965), including episodes of variant or vasospastic angina. Periods of arousal during sleep, even in the absence of overt wakefulness (such as k-complexes on the EEG) may also elicit bursts in sympathetic activation (Somersetal., 1993).

Deep sleep is also associated with an increase in glymphatic (glial-dependent lymphatic transport) drainage of the brain via a perivascular ‘pseudo-lymphatic’ complex, mediated by aquaporin 4 channels. Understanding of this system is evolving and the current state of knowledge, summarized below, is well described (Jessen et al., 2015; Plog & Nedergaard, 2018; Reddy & van der Werf, 2020). What is known is that clearance of metabolic waste, including amyloid beta and tau protein aggregations (linked to an increased risk of Alzheimer’s disease), from the brain via the lymphatics occurs primarily during sleep, particularly deep sleep. The involvement of the sympathetic nervous system is key in that the reduction of sympathetic activation during N3 or deep sleep is associated with expansion of the brain’s extracellular space, with consequent attenuated resistance to fluid flow. The slow oscillatory brain waves help generate flow in interstitial spaces, increasing glymphatic clearance. Hence conditions of increased sympathetic activation during sleep, as is seen during OSA and sleep restriction, described below, conceivably blunt glymphatic flow during sleep, potentially attenuating clearance of waste and predisposing to neurodegeneration such as is seen in Alzheimer’s.

This coordination between sleep stage and sympathetic outflow is disrupted during disordered sleep such as with sleep apnoea. There are two major types of sleep apnoea. First, OSA, which arises from partial or total occlusion of the upper airway during inspiration, with apnoea occurring despite very strenuous efforts to breathe. OSA is especially marked during REM sleep, in part because the REM-related loss of muscle tone increases the collapsibility of the upper airway during inspiration. Second, central sleep apnoea (CSA) is apnoea secondary to the absence of the drive to breathe, due to a range of potential causes including low levels of arterial CO_2 and respiratory centre immaturity or damage. While CSA is a trigger for increased sympathetic activation, it is during OSA, due to the often severe levels of nocturnal hypoxia, that sympathetic activation and its consequences are most evident (Somers et al., 1995). Obstructed breathing may induce apnoeas lasting up to a minute or sometimes longer. The reduction in arterial oxygen and the accompanying increase in arterial CO_2 activate both the peripheral chemoreceptors in the carotid sinus and the central chemoreceptors in the brainstem. These receptors normally elicit increases in sympathetic outflow and hyperventilation, with the stretch of the pulmonary afferents also serving to tamp down the sympathetic activation (Somers et al., 1989). However, with obstructive apnoea, there is no inspiratory stretch of the pulmonary afferents, so that sympathetic activation is unfettered, resulting in profound activation, with consequent vasoconstriction and BP surges as high as 240/130 mmHg during sleep (Fig. 6) (Somers et al., 1995). Note that peripheral chemoreflex activation also elicits cardiac vagal activation, also inhibited by stretch of the pulmonary afferents (Somers et al., 1989). Similarly, during obstructive apnoea, absence of the inhibitory influence of the pulmonary afferents results in marked cardiac vagal activation, with profound bradyarrhythmias sometimes occurring simultaneous with the sympathetic activation to peripheral blood vessels (Somers et al., 1992).

Nocturnal sympathetic activation in OSA carries over into daytime sympathetic activation, which may contribute to the increased prevalence of hypertension in OSA. Interestingly, administration of 100% oxygen to normoxic patients with OSA lowers both sympathetic activity and BP, suggesting that tonic chemoreflex activation even during daytime normoxia

may contribute to daytime sympathetic activation and high BP in patients with OSA (Narkiewicz et al., 1998).

While OSA is a well-known driver of sympathetic activation, recent data suggest that sleep insufficiency, frequently linked to a heightened risk for incident hypertension, may also contribute to increased sympathetic drive. In a randomized crossover study of 20 healthy young subjects, 9 days of restricted sleep (consisting of 4 h of sleep per night) were compared to 9 days of control sleep (up to 9 h of sleep per night) (Covassin et al., 2021). Restricted sleep resulted in an approximate 30% increase in early morning levels of plasma noradrenaline. Sleep restriction also elicited significant increases in BP during sleep, especially marked in women.

Questions and controversies

- What are the mechanisms underlying neuronal dysfunction in chronic obstructive sleep apnoea, and is there a therapeutic role for neuromodulation?
- How does the remodelling of cardiac autonomic control systems impact cardiovascular function in chronic OSA?
- What are the mechanisms of cardiovascular dysfunction that persist in spite of following effective treatment for sleep disordered breathing?

Influence of chronic intermittent hypoxic mechanisms on the autonomic nervous system in sleep apnoea.

Sleep disordered breathing (SDB)-specific consequences such as chronic intermittent hypoxia (CIH) contribute to changes in ANS function which result in evolution of cardiac structure, cardiac remodelling and functional alterations over time leading to adverse cardiovascular outcomes. Those with OSA have a high risk of development of hypertension, myocardial ischaemia and heart failure. ANS dysfunction characterized by sympathetic overactivation, reduced baroreflex sensitivity and blunted HRV is inherent to OSA and represents a key pathophysiological mediator. CIH, a hallmark of SDB, exerts long-term adaptations to myocyte ion channel currents thereby sensitizing the heart to episodic autonomic surges. CIH in murine models results in direct neuroanatomical effects of the sympathetic nervous system including intrinsic cardiac ganglia neuronal aberrant axonal patterning and increased density, tortuosity of catecholaminergic axons and increased atrial wall thickness (Bizanti et al., 2024). In addition to these effects on the sympathetic nervous system, effects of SDB on the parasympathetic nervous system have been described. Heart rate response to electrical stimulation of the vagal efferent nerve is increased following CIH and results in structural remodelling of the vagal cardiac axons and terminals in the cardiac ganglia as well as the cardiac principal neurons (Cheng, 2017). Baroreflex control of the heart rate is reduced in CIH with cardiac motor neurons in the nucleus ambiguous projecting to the cardiac ganglia identified to play a key role (Cheng et al., 2004). Intermittent hypoxia during the immediate post-natal phase induces a long-term reduction in heart rate baroreceptor control underscoring a developmental window of vulnerability.

Autonomic nervous system in sleep apnoea and cardiovascular outcomes.

The role of ANS alterations in OSA and cardiovascular implications have perhaps been best described in heart failure and cardiac arrhythmias. In heart failure, central sleep apnoea occurs most predominantly relative to other cardiovascular outcomes and is accompanied by repeated bursts in sympathetic nervous system activation (Costanzo et al., 2015; van de Borne et al., 1998). Autonomic fluctuations vary according to phase of ventilation with direct measures of muscle sympathetic nerve activity increasing during the central apnoeic phases and reduced during hyperventilation phases (van de Borne et al., 1998). Intermittent hypoxia and repetitive microarousals sine qua non with central respiratory events synergistically operate to chronically upregulate sympathetic nervous system activation (Tamisier et al., 2011) further augmenting the sympathetic over-activation inherent to heart failure. This then leads to increased vulnerability to cardiac arrhythmogenesis (Triposkiadis et al., 2009) and sudden cardiac death (Brunner-La Rocca et al., 2001). Treatment of Cheyne–Stokes respirations and central sleep apnoea with continuous positive airway pressure improves the activated sympathetic nervous system state resulting in reduced urinary and plasma noradrenaline concentrations (Naughton et al., 1995).

ANS fluctuations in OSA occurring longitudinally also contribute to a vulnerable atrial substrate by atrial hyperinnervation along with a downregulation of atrial cholinergic innervation in AF (Deneke et al., 2011; Sun et al., 2017). The electrophysiological remodelling perpetuates enhanced AF inducibility and duration of episodes in response to CIH (Yang et al., 2019). The counterbalance of sympathetic hyperinnervation in AF initiation because of respiratory event episodes and acute increases in parasympathetic activity during these events appear to favour the over-riding influence of the parasympathetic nervous system. Specifically, increased sensitivity of parasympathetic activation in AF is notable and further amplified in OSA (Bober et al., 2018). The reduction in the atrial effective refractory period inherent to OSA in experimental animal models is more strongly driven by muscarinic rather than β-adrenergic inhibition resulting in favourable effects of reduced AF inducibility, ectopy and recurrence (Zhao et al., 2014). The differential density of β_1-adrenoceptors *versus* M2 receptors may contribute along with differences in ion channel expression (Bober et al., 2018; Zhao et al., 2014) including upregulation of the G-protein-gated potassium channels responsible for the acetylcholine-activated inward potassium current, I_{KACh}, which is influenced by M2 receptor activation reflective of parasympathetic vagal control, that is, reduction in action potential duration due to hyperpolarization (Zhang et al., 2020). The autonomic dysfunction of OSA also exerts negative influences on cardiac structural remodelling characterized by necrosis of cardiomyocytes, oenema and downregulation of connexin-43 all of which were mitigated with cardiac sympathetic denervation in a rat model. Beta blockade resulted in reduced apoptosis and fibrosis via inhibition of mitogen-activated protein kinase (MAPK) with MAPK/extracellular signal-regulated kinase signalling recognized to contribute to cardiac apoptosis and fibrosis (Li et al., 2015; Yang et al., 2019).

Questions and controversies

- Could the lack of benefit from treating central sleep apnoea (CSA)–Cheyne–stokes respiration (CSR) in systolic heart failure be attributed to the possibility that CSR serves as an adaptive and protective response to heart failure?
- Might the variability in the effectiveness of treating CSA–CSR with positive airway pressure devices be influenced by the specific algorithms these devices use, potentially leading to variable or even deleterious effects on outcomes?
- Are the treatment outcomes for CSA–CSR in systolic heart failure different between patients with severe heart failure (New York Heart Association (NYHA) class 3 and 4) and those with less severe stages (NYHA classes 1 and 2)?
- Could the absence of clear cardiovascular benefits from treating obstructive sleep apnoea (OSA) be because only sleepy OSA patients, who are often not included in long-term randomized controlled trials, are at risk for cardiovascular events?
- Is the ineffectiveness of continuous positive airway pressure (CPAP) therapy in providing cardiovascular benefits for OSA patients due to inadequate adherence to the therapy?
- Are the pathological processes underlying OSA not reversible by CPAP therapy, especially when the treatment is initiated years after the onset of OSA?

Autonomic testing

Overview of autonomic function testing.

Several methods are available to assess autonomic function in humans. Autonomic function is the composite response to neural activity that originates at sensory afferents (baroreceptors, chemoreceptors, central command/mental stress, renal and other visceral afferents) and that is integrated in CNS nuclei that ultimately regulate reciprocal sympathetic and parasympathetic outflows that reach end-organs through efferent noradrenergic and cholinergic fibres. Noradrenergic fibres release noradrenaline in a tightly regulated and highly efficient process. Only about 10% of noradrenaline spills over into the circulation where it can be measured. Plasma noradrenaline is a rough indicator of sympathetic outflow and is elevated in cardiovascular diseases such as hypertension and heart failure where it is an index of bad prognosis (Grassi, 2021). Plasma levels of the stable metabolites normetanephrine and metanephrines are specific biomarkers of pheochromocytoma (Eisenhofer et al., 2003). Simultaneous measurement of plasma noradrenaline and its intraneuronal metabolic dihydroxyphenylglycine provides an indirect but clinically useful indicator of noradrenaline reuptake which can be altered in disease states (Robertson et al., 2001; Rumantir et al., 2000; Schlaich et al., 2003). Regional noradrenaline synaptic spillover into the circulation can be measured using a classical dilution method by infusing labelled noradrenaline and selectively sampling venous outflow and is altered in obesity and hypertension (Lambert et al., 2007). Unfortunately, this technique is no longer available because clinical-grade labelled noradrenaline is no longer manufactured.

Sympathetic nervous system assessment techniques.

Efferent sympathetic outflow can be recorded directly from postganglionic noradrenergic fibres innervating muscle vasculature (MSNA), which are under tight baroreflex control and reflect blood pressure regulation relevant to cardiovascular diseases such as obesity, hypertension and heart failure (Abrahao et al., 2002; Grassi et al., 2000, 2019). Whereas most studies have measured multiunit recordings, single-unit MSNA analysis is technically demanding, but provides more detailed information regarding central sympathetic firing (Lambert et al., 2011; Macefield & Wallin, 2018). Similar information can be extracted from multiunit recordings using wavelet denoising classification of action potential waveform classes (Brychta et al., 2007).

Parasympathetic nervous system monitoring.

By comparison, there are no techniques available that reliably measures parasympathetic nerve traffic or plasma levels of acetylcholine that reflect parasympathetic cardiovascular regulation. Cardiovagal function, however, can be estimated by measuring its effects on heart rate modulation, that is, HRV. HRV can be measured in the time domain, in the frequency domain and using non-linear methods. Several indices have been standardized (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and used clinically and in research. HRV in the high frequency domain reflects parasympathetic cardiac modulation and its reduction is associated with hypertension and heart failure and predicts adverse cardiovascular outcomes (Faber et al., 1996; Liao et al., 1996; Schroeder et al., 2003; Stein et al., 2005). Similarly, high frequency variability of blood pressure reflects sympathetic pressure modulation of blood pressure (Diedrich et al., 2003). Finally, it is now possible to use functional MRI, coupled with MSNA measurements, to identify areas of the brain involved in the generation and modulation of sympathetic outflow (Macefield & Henderson, 2019).

Dynamic testing of autonomic reflexes.

We have reviewed so far methods that test autonomic function at rest, and how they are useful clinical measurements of cardiovascular health and disease. More information can be obtained if autonomic afferents are stimulated while measuring the efferent function. Various stimuli can be used to disrupt autonomic function. Upright posture, triggered either by active standing or passive tilt table, induces gravitational volume shift from the thorax to the lower body. This venous pooling decreases stroke volume and induces compensatory sympathetic activation. Similar volume shifts can be induced by exposing the lower body to negative pressure using an air-tight chamber. The Valsalva manoeuvre produces similar fluid shifts in a transient and dynamic manner. Monitoring for changes in blood pressure in heart rate or MSNA can be used to calculate the sensitivity of the cardiovagal and sympathetic baroreflex, respectively. A more traditional method to measure baroreflex gain has been to pharmacologically induce changes in blood pressure (typically phenylephrine and nitroglycerine) to correlate with changes in heart rate interval and more recently MSNA. Finally, baroreflex gain can also be assessed non-invasively during continuous blood pressure monitoring by examining ‘spontaneous’ sequences of rising or falling blood pressure and corresponding reciprocal changes in heart rate intervals (Diaz & Taylor, 2006;

Laude et al., 2004). Each of these methods have advantages and disadvantages, but in general baroreflex sensitivity to control of heart rate is impaired in various cardiovascular diseases including obesity, hypertension, coronary vascular disease, post MI and heart failure (Chapleau, 2023).

One limitation of these approaches is the ‘closed loop’ nature inherent to human studies; that is, any change in blood pressure we induce will be instantaneously counteracted by the same baroreflex whose function we are trying to measure. An approximation of an open loop system can be obtained by applying random sequences of positive pressure and negative suction to the neck to stimulate the carotid baroreceptors in relative isolation (Akimoto et al., 2011; Fadel et al., 2003).

Standardized stress testing for autonomic response.

Other stressor can be used to investigate specific autonomic reflexes relevant to cardiovascular disease. Mental stress can be standardized using the Stroop test (a mismatch between colour names and their actual colours shown in a screen), mental arithmetic or cold pressor test is. Sustained handgrip followed by circulatory arrest assesses the contribution of muscle mechanoand chemo-receptors to autonomic reflexes. Off-axis chair rotation can be used for sinusoidal stimulation of vestibular receptors. In each case, simultaneous monitoring of MSNA provides useful information on autonomic function. Of note, acute sympathoexcitatory stress is highly predictive of the future risk of hypertension (Matthews et al., 2004). It should be noted that even if the application of these stressors is ‘standardized’, the magnitude of stress perception can vary between individuals (Callister et al., 1992; Joyner & Casey, 2015; Roddie, 1977).

Experimental techniques in autonomic research.

Acute withdrawal of autonomic function by administration of the ganglion blocker trimethaphan has been used to assess the contribution of autonomic function, similar to the use of hexamethonium in animal research. Acute autonomic withdrawal is associated with reversal of endothelial dysfunction (Gamboa et al., 2016), improvement of insulin sensitivity (Gamboa et al., 2014), and near normalization of blood pressure in obesity hypertension but not in models of non-neurogenic hypertension (Shibao et al., 2007). Unfortunately, this technique is available in only a handful of laboratories because trimethaphan is no longer manufactured.

An exciting development in the field is the application of ultrasound-guided microneurography to record from the cervical vagus nerve adjacent to the carotid artery. In proof-of-concept studies investigators have been able to identify multiunit recordings from post-ganglionic efferent vagal axons innervating the heart (Patros et al., 2022).

Summary and future directions in autonomic testing.

In summary, there is a wide spectrum of methods that assess autonomic function. At one end are methods that selectively stimulate specific afferents (e.g. white noise neck pressure and suction sequences) coupled with precise efferent recordings (e.g. MSNA), which are best suited for laboratory neurophysiological research. At the other end are methods that

can be applied to clinical settings and population research (e.g. HRV). Importantly, these indices correlate with cardiovascular disease and can predict adverse outcomes. Continuing to develop these important tools is necessary for advancing our understanding of the role of autonomic function in health and disease.

Risk stratification

Autonomic dysfunction and sudden cardiac death risk.

The role of the ANS in the pathogenesis of sudden cardiac death (SCD) is well established based on experimental studies and clinical studies showing an increased risk of SCD with sympathoexcitation and a reduction in SCD with β-adrenergic blockers in patients with heart failure and those who have suffered a MI.

Current non-invasive diagnostic approaches.

The realization of this crucial role for the ANS in the pathogenesis of SCD has led to the development of a plethora of non-invasive diagnostic tests to help define the ANS-related risk. These include evaluation of HRV, heart rate recovery after exercise, baroreflex sensitivity and heart rate turbulence, among others (Lahiri et al., 2008).

Limitations of existing autonomic markers.

While these tests have been shown to both reflect ANS activity and provide prognostic information on a population level, none has proven to be robust enough to be incorporated into clinical practice for assessment of individual risk. For example, low HRV was shown to be associated with increased risk of SCD in the Atherosclerosis Risk in Communities Study (Maheshwari et al., 2016). Each standard deviation decrement in the measured HRV parameters was associated with increased SCD risk, the most prominent increase being 27% for the low frequency power. The incident rate of SCD over a median 13-year follow-up was 1.37 per 1000 person-years in this population. While a 27% increased risk seems substantial, given the overall low risk, this increment does not provide enough individual risk stratification to alter clinical management. Nevertheless, further attempts atidentifying novel risk predictors have continued (Jørgensen et al., 2015), but with only marginal improvement. It is clear that novel strategies are required.

Anatomical and functional considerations in cardiac autonomics.

Given the important role of the ANS in the pathogenesis of SCD, it is necessary to understand why current risk stratification approaches focused on cardiac autonomics have not yet been effective in clinical use for prediction of SCD. There are several potential explanations that may all contribute to the challenge of SCD risk stratification with tests of cardiac autonomic function. First, while ANS dysfunction is associated with SCD, it is also associated with mechanisms of death other than SCD. Without adequate specificity for SCD, risk markers will not be clinically useful for SCD risk stratification. It is also important to consider that many of the tests that have been proposed focus on the autonomic input to the sinus node. The anatomical and functional innervation of the sinus node differs from that of the ventricle, making estimation of ventricular autonomic effects by those on the sinus node unreliable (Kannankeril & Goldberger, 2002); for arrhythmic SCD risk prediction, cardiac

autonomic effects on the ventricle are likely more relevant than those on the sinus node and should therefore be the focus for further development.

Challenges in autonomic risk stratification for sudden cardiac death.

It is also important to consider whether autonomic innervation and/or autonomic function need to be considered in the new risk stratification paradigm. While clinical imaging of cardiac sympathetic innervation is available, to date most efforts on risk stratification for SCD have focused on non-invasive tests of autonomic function. Finally, SCD is a unique event, seemingly a stochastic event, but is likely deterministic. Our evolving understanding of the complex, multilevel modulation of cardiac autonomic tone (Fukuda et al., 2015) with extensive feedback controls establishes a new paradigm for risk prediction related to autonomic dysfunction. Any individual's autonomic activity functions over a broad range of conditions, ranging from prominent parasympathetic effects at rest and at night to periods of sympathoexcitation during exercise. Across this spectrum of autonomic input to the heart, there are feedback loops and controls to maintain autonomic homeostasis. The precise defects in autonomic regulation – in location, intensity and number – that are required to trigger SCD are unknown. As even patients at high risk for SCD, with abnormalities in HRV and other established autonomic risk markers, experience constant autonomic modulation, be it by exercise, emotional changes, diurnal or seasonal changes, or others, there must be some other unmeasured constellation of factors that conspire to form the autonomic trigger leading to the singular event of SCD. The challenge for the future is to expand from the paradigm of simple autonomic risk factors for risk stratification for SCD to more complex pathways. Better understanding of the autonomic triggers for SCD could help in the design of better autonomic SCD risk stratification tools.

Innovative diagnostic and therapeutic approaches.

The feasibility of developing new diagnostic paradigms can be gleaned from the successful use of interventional procedures designed to modulate ANS activity that impact ventricular arrhythmias and SCD. Cardiac sympathectomy was first used to treat long QT syndrome (LQTS) and has remained an important therapeutic option (Dusi et al., 2022) for protection against serious ventricular tachyarrhythmias that has withstood the test of time. Cardiac sympathectomy has been extended to patients with structural heart disease and recurrent ventricular tachyarrhythmias also with significant benefit (Muser et al., 2017). While clinical studies have not demonstrated reduction in SCD with spinal cord stimulation, there are animal studies that provide interesting data in pigs (Howard-Quijano et al., 2021) and rabbits (He et al., 2023). In a porcine infarction model, vagal nerve stimulation (Hadaya et al., 2023) attenuated ventricular arrhythmias and electrical heterogeneity in the infarct border zone. Better definition of the 'defects' that are being repaired by these interventions can also help in the design of better autonomic-focused SCD risk stratification tools.

Conclusion and implications for clinical practice.

In summary, there is an intimate relationship between the activity of the ANS and SCD. Current approaches have identified general markers defining cardiac autonomic effects that have prognostic information that lacks specify and discrimination. Improved understanding of the anatomical and functional activity of the cardiac ANS and its response to external

manipulations that improve arrhythmia outcomes can serve as the basis for the development of more autonomically focused risk stratification tools that will have adequate predictive value for SCD.

Clinical management

Cardiac sympathetic denervation

i. *Channelopathies.* The use of left CSD, resection of the lower half or third of the left stellate ganglion and the second through fourth left thoracic sympathetic ganglia, first reported more than a century ago, is now established for congenital LQTS (Moss & McDonald, 1971; Schwartz et al., 1975) and catecholaminergic polymorphic ventricular tachycardia (CPVT) (De Ferrari et al., 2015; Wilde et al., 2008). Sympathetic activation is central to arrhythmogenesis in both conditions. Although CSD was first used more than a century ago by Jonnesco (as reviewed by Schwartz, 2014), studies by Estes and Izlar (1961) and Zipes et al. (1968) reintroduced CSD to the cardiac arrhythmia community. The rationale for CSD in LQTS and CPVT is the acute actions of sympathoexcitation (largely via release of noradrenaline and its co-transmitter, NPY) on cardiac electrophysiological function (dispersion of repolarization and enhanced intracellular calcium, respectively). In a study reporting on the use of LCSD in 147 patients with LQTS (Schwartz et al., 2004), the mean yearly number of cardiac events per patient dropped by 91%. The percentage of patients with >5 cardiac events declined from 55% to 8%, while post-LCSD count of shocks decreased by 95%. Of note, among 51 genotyped patients, left CSD appeared more effective in LQT1 and LQT3 patients. Thus, in these patients, left CSD, typically performed by minimally invasive video-assisted thoracoscopic surgery can prevent the occurrence of dangerous ventricular arrhythmias in most patients, including children (Collura et al., 2009). Importantly, the wealth of data supporting left CSD in LQTS has supported its inclusion as a class I therapy in the guideline document for managing patients with ventricular arrhythmias (Al-Khatib et al., 2018), although common practice is that LCSD is primarily indicated for patients with recurrent implantable cardioverter-defibrillator (ICD) therapies or those who experience syncope despite adequate doses of beta-blocker therapy (Schwartz & Ackerman, 2013).

ii. *Structural heart disease.* Although the first application of CSD as reported by Jonnesco was performed bilaterally for a patient with structural heart disease, subsequent use of CSD for structural disease was primarily left sided (Lloyd et al., 1974; Nitter-Hauge & Storstein, 1973; Schoonmaker et al., 1975; Schwartz et al., 1992; Zipes et al., 1968). Advances in understanding of the adverse effects of adrenergic activation following MI and the advent of pharmacological agents to mitigate neurohormonal activation (i.e. angiotensin receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACE-I)) (Hjalmarson, 1997; Kober et al., 1995), the invasive nature of CSD rendered it less attractive.

While these pharmacological agents and catheter-based ablation of ventricular tachycardia led to impressive control of VT/VF in structural heart disease, a sizeable proportion of patients remained recalcitrant to these therapies, with continued VT/VF episodes and ICD therapies. Left CSD was applied in this patient population with positive results, albeit limited efficacy, particularly when compared to use of thoracic epidural anaesthesia (Bourke et al., 2010), which achieved superior control of ventricular arrhythmias in structural heart disease. Arrhythmia recurrences in patients with structural heart disease undergoing LCSD for VT spurred the addition of right CSD in patients with prior left CSD and recurrence, as well as a priori bilateral CSD (BCSD) in patients with structural heart disease. The first case series of BCSD for structural heart disease showed positive results (Ajijola, Lellouche et al., 2012), and bilateral CSD was superior to left CSD alone when compared directly in a similar patient population, albeit retrospectively (Vaseghi et al., 2017).

Questions and controversies

- What is the contribution of cardiac de-afferentation to the success of cardiac sympathetic denervation?
- Which clinical features are most important in patient selection for cardiac sympathetic denervation?
- What is the role of sympathetic denervation in patients with heart failure or recalcitrant angina? Which biomarkers best predict procedural response and long-term efficacy?

Neural remodelling in following cardiac injury has been reviewed in detail in the prior white paper and in the basic (Habecker, 2025) and translational (Herring, 2025) white papers and will not be discussed at length here. However, the mechanisms of CSD in patients with structural heart disease appears distinct from those in patients with LQTS and CPVT. In structural heart disease, remodelling of bilateral stellate ganglia (Ajijola et al., 2017) driven primarily by chronic TRPV1 afferent activation (Wang, Wang et al., 2014; Yoshie et al., 2020) and other mechanisms promote dysfunctional cardiac sympathetic activation by both stellate ganglia and presumably T2–T4 ganglia as well. Importantly, since these TRPV1 afferent fibres traverse the sympathetic chain en route to the dorsal root ganglia, bilateral CSD interrupts cardiac afferent neurotransmission and its consequent sympathetic drive to the heart. Additionally, the cell bodies of post-ganglionic sympathetic neurons innervating the heart are distributed within the stellate ganglion and middle cervical ganglion. Bilateral CSD partially interrupts efferent sympathetic drive, since it targets the lower half or third of the stellate ganglion. The benefit of CSD, with respect to interrupting efferent sympathetic drive, may be mediated by interrupting sympathetic local circuit neurons and some post-ganglionic efferent sympathetic neurons which remodel in the setting for chronic structural heart disease (Fig. 5). Importantly, a large proportion of cardiac sympathetic neurotransmission occurring via the MCG and upper stellate ganglia is spared.

Thoracic epidural anaesthesia and stellate ganglion blockade.

Anaesthetic interventional techniques such as thoracic epidural anaesthesia and stellate ganglion block allow modulation of sympathetic tone to the heart. In patients with

sympathetically triggered arrhythmias, these neural modulation approaches have provided therapies for reducing the arrhythmia burden.

Selective neuraxial modulation of sympathetic signalling to the heart using a high thoracic epidural anaesthesia (TEA) technique is an effective antiarrhythmic approach in animals and humans (Bourke et al., 2010; Kamibayashi et al., 1995; Mahajan et al., 2005; Oka et al., 2001). In patients with refractory VT unresponsive to medical therapy and cardiac ablation, Bourke et al. (2010) demonstrated that TEA was highly effective in reducing the VT burden in 75% of the patients (CI 51%–91%, $P = 0.05$). Similarly, Oka et al. (2001) showed that in patients undergoing lung surgery, the incidence of postoperative supra-ventricular tachyarrhythmias was significantly lower in the group receiving TEA when compared to controls (1/23 *vs.* 7/25, respectively, $P = 0.05$).

TEA is performed by percutaneously administering local anaesthetics in the thoracic epidural space – a limited sympathectomy of the T1–T5 spinal segments is created by pharmacological block at the level of the spinal cord and spinal roots (Bourke et al., 2010; Mahajan et al., 2005). Since the spread of the drug is not restricted in the epidural space, TEA can block both afferent and efferent sympathetic signalling of the right and left spinal roots, significantly reducing the spinal cord influences. At the level of the heart, the antiarrhythmic effects of TEA are seen due to changes in myocardial excitability, including lengthening of repolarization and prolongation of refractory periods (Meissner et al., 2001). In patients with ischaemic heart disease, regional sympathetic block from TEA not only reduces ischaemic pain but also preserves coronary perfusion with the effect most pronounced in stenotic vessels (Nygard et al., 2005; Olausson et al., 1997). These results demonstrate the protective effects of TEA in mitigating ventricular arrhythmias mediated by increased sympathetic tone. While the effectiveness of TEA is evident, its therapeutic use is limited by its short-term use in patients.

Stellate ganglion block (SGB) involves the delivery of anaesthetic agents via percutaneous approaches to peripheral sympathetic ganglia (Ganesh et al., 2020). SGB reduces sympathetic output and consequently cardiac excitability is attenuated (Loyalka et al., 2011; Nademanee et al., 2000; Patel, Priore et al., 2011). In a case series, cardiac sympathetic blockade, including SGB, exhibited greater antiarrhythmic effect compared to guidelines recommending advanced cardiac life support (Nademanee et al., 2000). Further, survival in patients who underwent sympathetic blockade was superior to those patients treated with antiarrhythmic drug therapy. The mechanisms of action of SGB likely include attenuation of persistent cardiac afferent activation, as well as reduced efferent sympathetic output. Although the efficacy of SGB is documents in post-infarction ventricular arrhythmias (Garcia-Moran et al., 2013), the short-term effects can be limiting, with some studies relying on recurrent SGB for several months (Hayase et al., 2013). While randomized placebo controlled studies of SGB have not been performed, existing studies suggest a favourable safety profile with significant antiarrhythmic effects (Chouairi et al., 2024; Fudim, Qadri et al., 2020; Savastano et al., 2024).

Questions and controversies

- Where in advanced cardiac life support algorithms should TEA and SGB be placed in resuscitation and treatment of electrical storm?
- Do TEA and SGB predict efficacy of cardiac sympathectomy?
- What factors determine whether short or long-acting anaesthetics should be used for TEA and SGB, and in which patients?

SGB has some limitations. Unlike surgical sympathetic denervation, which selectively removes only the lower third of the stellate ganglia along with the upper thoracic sympathetic chain, percutaneous LSG block with local anaesthetics is non-specific, and typically abolishes conduction to the heart as well as to the head, neck and diaphragm. This also limits the concurrent application of left and right SG, unless the patients are being mechanically ventilated.

Vagal nerve stimulation in heart failure.

In principle, VNS can be performed with open loop or closed loop systems. In the former the stimulation protocol is essentially independent from the evoked biological response while in the latter, the stimulation parameters are influenced by a continuously monitored biomarker (e.g. heart rate in cardiac patients). Closed loop systems are conceived to mimic, albeit with an obviously minor degree of integration, the principle of functioning of an animal or human feedback neuronal network, including biomarkers, sensors and data processing algorithms.

The first study performed in patients with heart failure, the multicentre open label CardioFit study (de Ferrari et al., 2011; de Ferrari, 2014), found a potential benefit of VNS among patients with heart failure with reduced ejection fraction (HFrEF). The study enrolled 32 patients in NYHA class II–III on optimal medical treatment with LVEF ≤ 35%; 24-h Holter average sinus rate of 60–110 bpm who were capable of performing a 6-min walk test. The CardioFit system (BioControl Medical Ltd, Yehud, Israel) was a neurostimulator closed loop system, sensing heart rate via a standard intracardiac electrode and delivering stimulation at a variable delay (70–325 ms) from the R wave. On the average, stimulation intensity was 4.1 ± 1.2 mA and duty cycle (percentage of time with stimulation on) 21 ± 5%.

There were significant improvements in NYHA class, quality of life, 6-min walk test, LV ejection fraction (from 22 ± 7% to 29 ± 8%) and LV systolic volumes at 6 months. These improvements were maintained (and even magnified) at 1 year (de Ferrari et al., 2011). Two serious adverse events were considered device-related: postoperative pulmonary oedema and need for surgical revision. Expected non-serious device-related adverse events (cough, dysphonia, stimulation-related pain) occurred early but were reduced and disappeared after stimulation intensity adjustment. The promising outcomes of this proof-of-concept study led to additional clinical trials.

ANTHEM-HF (autonomic regulation therapy for the improvement of left ventricular function and heart failure symptoms) was an open-label phase II multicentre study performed in India that assessed the feasibility, safety and tolerability of autonomic

regulation therapy (ART), and compared right *versus* left vagal nerve stimulation in 60 NYHA II–III patients with LVEF ≤ 40% (Premchand et al., 2014). It was an open loop system without intracardiac electrode. Stimulation parameters were systematically adjusted over a 10-week titration period to a pulse width of 250 μs and a pulse frequency of 10 Hz in all patients. After 6 months of ART, the study confirmed the feasibility and safety of the procedure. At the end of 6 months, significant improvements were seen in LVEF, LV end systolic diameter, HRV and Minnesota living with HF questionnaire and 6-min walk distance. NYHA class improved in 77% of patients. Overall, a modest trend was also observed towards a greater efficacy for the right-sided stimulation. An extension of the ANTHEM-HF patient follow-up for an additional 6 months (total of 12 months following titration) showed that the benefits of ART seen at 6 months persisted at 1 year with no further improvement (Premchand et al., 2016).

NECTAR-HF (neural cardiac therapy for heart failure study) was a randomized sham-controlled trial multicentre European phase II study in which all patients (NYHA II–III, LVEF < 35%) were implanted with a right-sided vagal stimulator without intracardiac electrode, and randomized 2:1 to an active group that had the device switched ‘on’ and an inactive group that had it switched ‘off’ for the first 6 months (de Ferrari et al., 2014; Zannad et al., 2015). The device, produced by Boston Scientific (Minneapolis, MN, USA) had shown favourable efficacy results in preclinical studies (Hamann et al., 2013). The frequency of stimulation was 20 Hz and the current intensity only reached an average of 1.3 ± 0.8 mA, limited by side effects. Of the 96 patients enrolled, 87 had paired data at 6 months for analysis. No change in any hard endpoint was observed between the two groups, although there were favourable changes in NYHA (62% of patients in the active group *versus* 43% in the inactive group improved NYHA class, $P = 0.032$) and in quality of life in the active group. However, the efficacy of blinding was incomplete among patients assigned to the active stimulation group. The 18-month follow-up after therapy was switched ‘on’ in the sham-control group at 6 months and remained ‘on’ in the active group throughout and agreed with the lack of significant effect on the primary endpoint (de Ferrari et al., 2017). However, a specific analysis developed to detect even extremely subtle changes of heart rate (invisible with traditional approaches) between the on and the off phases of nerve stimulation found that the stimulation affected the sinus node activity in only 12% of cases. This very low percentage was markedly lower than what was observed in preclinical studies, which showed significant effects on cardiac remodelling with the same device (Zannad et al., 2015).

Altogether, these first three trials all showed good safety for VNS, but obtained different efficacy results:

CardioFit and ANTHEM-HF showed a favourable effect, while NECTAR-HF was neutral. This discrepancy was considered to be due to the blinded nature of the latter trial as compared to the unblinded one in the first two studies and to the excessively low intensity of stimulation reached in NECTAR-HF (1.4 mA) (de Ferrari et al., 2017).

It should be underlined that ‘dosing’ of autonomic regulation therapy is complex, involving numerous variables including, among others, closed or open loop system, electrode location

and configuration, pulse frequency, amplitude and width, and stimulation duty cycle (de Ferrari & Schwartz, 2011). Ardell et al. investigated several combinations of frequency–amplitude–pulse width, defining ‘neural fulcrum’ as the operating point where a null heart rate response is reproducibly evoked during the on-phase of VNS (Ardell et al., 2017). Our overall understanding suggests that the ideal vagus nerve stimulation parameters should be mildly stronger than those defining the neural fulcrum.

In conclusion, vagus nerve stimulation for heart failure has a strong rationale and appears safe. Few small unblinded studies suggested favourable effects, while two larger studies failed to show a significant improvement compared to optimized medical therapy. Specifically, the most recent trial, ANTHEM-HFrEF, raised great expectations, but was unfortunately terminated early by the sponsor for a non-scientific reason. Although the original primary endpoint was not met, the revised win ratio was significantly in favour of vagal stimulation. This leaves open the possibility of a future reappraisal of this therapeutic option.

Vagal nerve stimulation in atrial fibrillation.

The role of the ANS in the pathogenesis of AF is well established (Hanna et al., 2021; Stavrakis, Nakagawa et al., 2015). While vagus nerve stimulation which markedly slows the heart rate induces AF (Liu & Nattel, 1997), paradoxically, low-level VNS, at stimulation intensities 10–80% of the threshold for heart rate reduction, suppressed AF in multiple animal models (Shen et al., 2011; Sheng et al., 2011; Yu et al., 2011, 2012). The antiarrhythmic effects of low-level VNS may be mediated through inhibition of neural activity in the cardiac autonomic ganglia (Yu et al., 2011) and stellate ganglia (Shen et al., 2013), resulting in anticholinergic or antiadrenergic effects, respectively (Sha et al., 2011). Moreover, the anti-inflammatory effects of VNS may also contribute to AF suppression (Stavrakis et al., 2017). In humans, low-level VNS exerted beneficial effects in a small, randomized sham-controlled clinical trial, suppressing post-operative AF and pro-inflammatory cytokines in patients undergoing cardiac surgery (Stavrakis et al., 2017). Nonetheless, implementation of low-level VNS for the suppression of atrial arrhythmias in clinical practice may be limited by an unfavourable risk–benefit ratio due to potential side effects, and poor patient tolerance associated with the implantation of the VNS device (Ben-Menachem et al., 2015), thus leading to the quest for a non-invasive option for VNS.

Transcutaneous vagus nerve stimulation.

Transcutaneous vagus nerve stimulation (tVNS) refers to application of electrical current at either the tragus or the cymba conchae, targeting the auricular branch of the vagus nerve (Butt et al., 2020; Peuker & Filler, 2002) (Fig. 7). The downstream targets of tVNS include vagal nuclei in the brainstem, such as the NTS, projecting to cortical, subcortical and cerebellar regions, as shown by functional MRI (Frangos et al., 2014; Yakunina et al., 2017). Notably, activation of these areas outlasted the duration of stimulation (Frangos et al., 2014), suggesting that short durations of therapy may result in long-lasting effects (Frangos et al., 2015; Koopman et al., 2016; Stavrakis, Stoner et al., 2020; Stavrakis et al., 2022). Another potential explanation of the ‘memory’ effect of tVNS is synaptic plasticity within the cardiac autonomic ganglia, that is, the ability to alter the strength of the synapses within these neural

structures (Ashton et al., 2018). It should be noted, however, that the minimum duration of tVNS that is required to improve clinical outcomes has not yet been elucidated. A potential benefit of tVNS over cervical VNS is that the latter may stimulate vagal sympathetic components (Seki et al., 2014), thus leading to unknown adverse events not encountered with the non-invasive approach (Deuchars et al., 2018). While the exact mechanisms are still not well understood, the beneficial effects of tVNS are likely due to its pleiotropic effects. Specifically, activation of afferent vagal projections increases central parasympathetic tone and attenuates the sympathetic outflow to the heart (Deuchars et al., 2018), while also exerting strong anti-inflammatory effects, which may also contribute to suppression of atrial arrhythmias (Stavrakis, Humphrey et al., 2015; Stavrakis et al., 2017; Stavrakis, Stoner et al., 2020). Moreover, tVNS has been shown to upregulate atrial connexins (Chen et al., 2015) and to attenuate the increase of nerve growth factor in the autonomic ganglia in canines (Yu et al., 2017). The extent to which each of these mechanisms contributes to suppression of atrial arrhythmias remains to be determined.

Preclinical studies of tVNS paved the way for human clinical trials (Yu et al., 2013). In a proof-of-concept study in patients with paroxysmal AF who presented for AF ablation, 1 h of tVNS at the tragus (prior to any ablation) significantly shortened pacing-induced AF duration, lengthened atrial effective refractory period and decreased serum inflammatory cytokines (Stavrakis et al., 2015a). In healthy volunteers, low-level tVNS increased HRV and reduced muscle sympathetic nerve activity, suggesting an anti-adrenergic effect (Clancy et al., 2014). In a subsequent randomized, sham-controlled clinical trial, chronic, intermittent tVNS (1 h daily) resulted in a significant 85% decrease in the median AF burden, assessed by a 2-week non-invasive ECG monitor at 6 months, compared to the sham stimulation, and without device-related side effects (Stavrakis, Stoner et al., 2020). However, at the individual patient level, the response to tVNS was variable across patients, highlighting that although tVNS is an emerging, promising modality for AF, the dosing and/or patient selection needs to be optimized before clinical adoption on a larger scale.

As noted above, optimization of stimulation parameters and/or patient selection is a critical component for the success of neuromodulation therapies (Stavrakis et al., 2020a). The different stimulation parameters used in tVNS studies may account for the heterogeneity in the results (Farmer et al., 2020). It was previously shown that a combination of a pulse width of 0.5 ms with a frequency of 10 Hz decreased heart rate more than other parameters (Badran et al., 2018). The caveat of such studies is that heart rate is determined by mixed inputs from the sympathetic and parasympathetic nervous system, and therefore the heart rate-lowering effect of tVNS may not necessarily correlate with arrhythmia suppression (Farmer et al., 2020; Stavrakis, Kulkarni et al., 2020).

Patient selection, based on a biomarker of response, is of the utmost importance in optimization of neuromodulation therapy outcomes (Stavrakis, Kulkarni et al., 2020). Unfortunately, there are no proven biomarkers of response to tVNS. Although HRV has been used as a biomarker in neuromodulation studies (Farmer et al., 2020), the use of HRV is limited by the fact that changes in HRV correlated with the effect of the ANS on the sinus node, and not necessarily with arrhythmia suppression (Stavrakis, Kulkarni et al., 2020). Other potential biomarkers include P wave alternans (Kulkarni et al., 2021) and NPY

(Stavrakis, Morris et al., 2020), which have been each been shown to predict responders to tVNS for AF in *post hoc* analyses of the TREAT AF study (Stavrakis, Stoner et al., 2020). Another potential biomarker may be the neurotrophic protein S100B, which is released from cardiac glial cells (Scherschel et al., 2019) and has been correlated with acute damage of the cardiac autonomic ganglia during AF catheter ablation, but has not been evaluated as a predictor of tVNS. Ultimately, tVNS for atrial arrhythmias may be implemented in a closed-loop system, where a biomarker is continuously detected by the tVNS device, and appropriate therapy is delivered based on changes in the biomarker. The development of probes capable of measuring neuropeptides (including NPY) in real time is a forward step in this direction (Kluge et al., 2022). Future research should focus on identifying biomarkers of response to tVNS to guide patient selection and optimize the therapeutic effect.

Questions and controversies

- What are the optimal stimulation parameters for maximizing the beneficial effect of vagal nerve stimulation and other neuromodulation therapies?
- Are there biomarkers of response to vagus nerve stimulation that can be used for patient selection?
- Would a closed-loop system, where stimulation is delivered in response to real-time detection of a biomarker or changes in autonomic tone, improve the optimization of vagal nerve stimulation?

Dorsal root ganglion stimulation.

The dorsal root ganglion (DRG) is a collection of neurons and cell bodies located in the lateral epidural space within the spinal foramen. It is located on the dorsal root and as such is a critical structure for the transmission of sensation from the periphery to the spinal cord (Fig. 8) (Krames, 2015). In humans, there are 31 pairs of spinal nerves that convey autonomic, sensory and motor information to or from the cord. The DRG can act as a filter to suppress or block afferent activity or as a propagator, especially in diseases such as neuropathic pain (Hanani, 2005). The role of the DRG in pain is out of the scope of this article but it is known that a number of cellular and electrical changes occur in the neuropathic pain condition. These include changes to the satellite glial cells (which signal using cytokines, ATP, bradykinins, etc.), as well as hyperexcitability in axotomized cells (Sapunar et al., 2005). In complex regional pain syndrome (CRPS) type 1, neuropathic pain may be generated and maintained, not just by sensory nerves alone, but by the sympathetic nervous system – so called sympathetically maintained pain (Price et al., 1998). It is perhaps unsurprising that clinical DRG stimulation is particularly efficacious in CRPS (Deer et al., 2017), and this may (at least partially) work using a degree of sympathetic downregulation (Sverrisdottir et al., 2020).

At present, radiofrequency lesioning and DRG stimulation (DRGS) are only routinely used for the treatment of pain. However, in CRPS, associated with autonomic changes such as swelling, altered skin blood flow and hair loss, both radiofrequency lesioning and DRGS improve these features in addition to the pain (van Buyten et al., 2015). Sverrisdottir et al. (2020) performed microneurography and directly measured MSNA in a cohort of patients

undergoing DRG stimulation for chronic neuropathic pain. The investigators found that efferent sympathetic activity significantly reduced with acute stimulation at a variety of levels. This effect was not well correlated with analgesic effects. Furthermore, baroreceptor sensitivity and heart rate remained unchanged, and the authors propose that the effects are likely to be due to local or spinal mechanisms on this basis. In three individuals with refractory essential hypertension pre-operatively, BP at long-term follow-up was within the normal range. DRGS reduced the low frequency power and increased the high frequency power, implying a reduction in sympathetic activity. The mechanism of these actions of DRG stimulation are unknown. Possibilities include modulation of the sympathetic chain via the rami communicates, or directly altering activity to the intermediolateral cell column mediating sympathetic changes in the spinal cord. Another possibility is via ventral root afferent fibres. Chung et al. (1986) studied the systemic arterial pressure response to stimulation of the stump of a transected spinal ventral root in the cat and concluded that afferent fibres in the ventral root course distally to the DRG and enter the spinal cord via the dorsal root. DRGS may alter this reflex. In a small number of patients with peripheral vascular disease, Chapman et al. (2021) showed not only improvement in pain scores, but increased blood flow to the peripheries, by measuring peripheral vascular resistance and transcutaneous oxygen pressure (TcPO2)t. The mechanisms underlying this are presumably via altered sympathetic outflow to preganglionic peripheral ganglia. This would be a similar pathway as involved in the Loven reflex in which vasodilatation is induced by nociception (Janig, 2021). The DRG is involved in the afferent part of this pathway.

Ganglionated plexus ablation for reflex syncope, atrioventricular block and sinus bradycardia–asystole.

Pre-ganglionic parasympathetic axons of the vagus nerve synapse onto the postganglionic cardiac parasympathetic neurons in the autonomic ganglia on the epicardium and then innervate the sinoatrial and the atrioventricular nodes (Jänig et al., 2006). Autonomic ganglia cluster in the following anatomical regions known as ganglionated plexi (GPs) (Armour et al., 1997): superior (anterior) right atrial GP (RSGP); posterior (inferior) right atrial GP (RIGP); superior left atrial GP (LSGP); posterolateral (inferior) left atrial GP (LIGP); and posteromedial left atrial GP (PMLGP). The vein of Marshall also provides parasympathetic fibres to surrounding left atrial structures and the coronary sinus (Ulphani et al., 2007). Ablation of these anatomical regions resulted in parasympathetic neuromodulation, which was demonstrated by heart rate increase, HRV reduction and making the heart non-responsive to atropine. Therefore, the potential therapeutic role of endocardial radiofrequency catheter ablation of GPs for treating conditions characterized by reflex syncope and vagally mediated atrioventricular block and sinus bradycardia–asystole was investigated by numerous groups (Aksu et al., 2016, 2019, 2020; Aksu, Gopinathannair, Bozyel et al., 2021; Aksu, Gopinathannair, Gupta et al., 2021; Aksu, De Potter et al., 2022; Aksu, Padmanabhan et al., 2022; Calo et al., 2021; Debruyne et al., 2018, 2021; Francia et al., 2023; Hu et al., 2019; Pachon et al., 2005, 2011; Qin et al., 2017; Rivarola et al., 2017; Sun et al., 2016; Piotrowski et al., 2023; Rivarola et al., 2023; Stec et al., 2023; Wileczek et al., 2023; Xu et al., 2022; Zhao et al., 2015). Although there is a high amount of interconnection between autonomic ganglia and GPs, the largest number and density of autonomic ganglia which supply nerves to the sinoatrial node are typically located at the

RSGP (Aksu, Gopinathannair, Bozyel et al., 2021; Pauza et al., 2000). Postganglionic nerves from the PMLGP, RIGP and vein of Marshall extend towards the interatrial septum and are thought to supply the atrioventricular node region (Aksu, Gopinathannair, Bozyel et al., 2021; Pauza et al., 2000; Ulphani et al., 2007). Physiological experiments indicated that surgical dissection of parasympathetic pathways to the atrioventricular node at the junction of the inferior vena cava and inferior left atrium eliminated the dromotropic effects of vagal stimulation without affecting the sinus rate response (Billman et al., 1989). On the contrary, surgical dissection of the fat pad overlying the right pulmonary vein–superior vena cava junction significantly attenuated negative chronotropic effects of vagal stimulation (Billman et al., 1989).

Reflex syncope describes syncope due to a specific trigger such as standing, pain or fear, carotid sinus syncope, and situational syncope evoking a variable combination of vasodepression and cardioinhibition (Brignole et al., 2018). Although cardioinhibition is often seen in younger individuals, vasodilatation is more prevalent in older age (Rivasi et al., 2021). While the vasodepressive phase is largely due to blood pooling in the abdomen and lower limbs via a reflex inhibition of the sympathetic system (Fuca et al., 2006), cardioinhibition interferes in the last minute via the vagus nerve resulting in an acceleration of the fall in systemic blood pressure due to a steep decrease in cardiac output, which leads to cerebral hypoperfusion and loss of consciousness (van Dijk et al., 2020). Similarly, a small group of patients have frequent episodes of symptomatic sinus bradycardia-arrest or variable degree atrioventricular block (AVB) even in the absence of syncope, which usually occur at rest and during sleep and disappear during exercise (Alboni et al., 2013; Sidhu & Marine, 2020). These forms of bradyarrhythmia are usually related to parasympathetic overactivity and are referred to as extrinsic, functional or vagally mediated. Ablation of GPs may mitigate parasympathetic overdrive on the sinoatrial and atrioventricular nodes and be used in selected patients with these vagally mediated bradyarrhythmias.

During the ablation procedure, the following three methods can be used for mapping of GPs: (1) high-frequency stimulation aiming to differentiate GP sites from the remaining atrial myocardium by evaluating a positive vagal response, which is characterized by immediate sinus bradycardia (increased R-R interval by 50%), transient ventricular asystole (>3 s) or atrioventricular block (Stavrakis, Nakagawa et al., 2015); (2) an electrogram-based approach that assumes that in the regions related to GPs, electrograms are characterized by highly fractionated intracardiac signals, contrary to the surrounding atrial myocardium that shows non-fractionated or less fractionated atrial potentials (Aksu et al., 2019); and (3) an anatomically guided approach based on the empirical ablation on the presumed anatomical location of the GPs as an adjunct to electrogram analysis or high-frequency stimulation, or as a stand-alone strategy (Aksu, Gopinathannair, Bozyel et al., 2021; Aksu, Gopinathannair, Gupta et al., 2021). Subgroup analysis of a recently published meta-analysis demonstrated that the technique used to identify GPs does not show any significant difference in freedom from syncope ($P = 0.206$) (Vandenberk et al., 2022). Comparative data for these GP mapping techniques are lacking and validation studies are needed.

After mapping of GPs, three different techniques have been applied for GP ablation: (1) a right-atrial approach (a unifocal approach focusing on the RSGP by using an anatomical

approach as a stand-alone strategy (Debruyne et al., 2018, 2021) and multifocal approach targeting RSGP, RIGP and PMLGP by using anatomical landmarks as an adjunct to electrogram analysis (Calo et al., 2021); (2) a left-atrial approach (four or five major GPs (LSGP, LIGP, MTGP, RSGP and RIGP were targeted by using high-frequency stimulation or anatomical approach; Hu et al. 2019; Sun et al. 2016); and (3) a bi-atrial approach (a whole or selected number of GPs were targeted via both atria). Different combinations of electrogram analysis, high-frequency stimulation, and anatomical landmarks were used to target GPs (Aksu et al., 2016, 2019, 2020; Aksu, Gopinathannair, Bozyel et al., 2021; Aksu, Gopinathannair, Gupta et al., 2021; Aksu, de Potter et al., 2022; Aksu, Padmanabhan et al., 2022; Pachon et al., 2005, 2011, 2020; Piotrowski et al., 2023). According to the published literature, although RSGP and PMLGP represent the main targets for parasympathetic denervation of the sinoatrial and atrioventricular nodes, respectively, and can be achieved via a right-atrial approach, right-atrial GP ablation was associated with a significantly lower freedom from syncope (81.5%; 95% CI 51.9%–94.7%; $P < 0.0001$) *versus* left atrial ablation only (94.0%; 95% CI 88.6%–6.9%) and biatrial ablation (92.7%; 95% CI 86.8%–96.1%) (Vandenberk et al., 2022). Thus, the bi-atrial approach is needed in some patients to achieve full and more durable parasympathetic neuromodulation.

After the first clinical application of GP ablation by Pachon et al. (2005), the modality has been adopted gradually by interested clinicians around the word. However, most of the clinical evidence has been accumulated from observational data. Furthermore, there are significant discrepancies between studies in terms of applied patient selection criteria.

Several observational and retrospective studies have shown the salutary effects of GP ablation not only in patients with a dominant cardioinhibitory response, but also in patients with pure vasodepressor syncope (Hu et al., 2019; Xu et al., 2022). Considering the intermittent nature of symptoms, expectation/placebo effects, and the complex pathophysiology with interindividual variability in patients with vasovagal syncope, there is a lack of a strong rationale for GP ablation in the presence of a dominant vasodepressor component.

The first case–control study assessed the long-term effect of GP ablation (51 patients) versus conservative therapy (50 patients) for vasovagal syncope with the dominant cardioinhibitory response (Aksu, De Potter et al., 2022). GP ablation was associated with a significantly lower risk of syncope recurrence (hazard ratio 0.23, 95% CI 0.03–0.99, $P = 0.049$) during a median follow-up of 22 months. Recently, a randomized controlled trial comparing GP ablation and conservative treatment recommended by current guidelines was published and showed 92% efficacy of GP ablation compared with 46% of optimal non-pharmacological treatment in patients with the dominant cardioinhibitory response (Piotrowski et al., 2023). Thus, based on the current literature, GP ablation should be tried to reduce syncope in younger patients, with severe, unpredictable, recurrent dominant cardioinhibitory response (spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest or AVB or >3 s asystolic syncope during tilt testing or spontaneous ECG-documented bradycardia <40 bpm for >10 s during spontaneous syncope) when non-invasive conventional therapies have failed to prevent syncope recurrences. GP ablation has also been studied for carotid sinus syncope and situational syncope in small case series.

Results of series with shorter follow-up appear to show efficacy (Francia et al., 2023; Miranda-Arboleda et al., 2023; Stiavnicky et al., 2020).

With regard to sinus bradycardia and atrioventricular block, while in patients with cardioinhibitory reflex syncope, bradycardia is restricted to the time of occurrence of syncopal episodes and the rhythm is normal outside these episodes, some patients may have frequent symptomatic episodes of sinus bradycardia or asystole or AVB, even in the absence of syncope. Some of these patients suffer from symptoms of fatigue, irritability, lassitude, inability to concentrate, lack of interest, forgetfulness and dizziness that sometimes greatly impairs their quality of life. Although, a clear cause–effect correlation between symptom and bradycardia is often difficult to prove in such settings, a vagally mediated nature of these bradyarrhythmias is suspected because bradycardia is intermittent. Clinical features, pharmacological manoeuvres or an electrophysiological study may help differentiate vagally mediated from intrinsic ones. Although no controlled trial has yet been performed in patients with sinus bradycardia and/or AVB, a few small observational studies and case reports have shown improvement of sinus function and atrioventricular conduction after GP ablation. However, the populations enrolled in these studies were very heterogeneous. Qin et al. (2017) studied the long-term effects of GP ablation in patients with symptomatic sinus bradycardia. Although patients of <50 years of age demonstrated significant relief on symptoms after GP ablation, the increase in heart rate was lower in patients >50 years of age, and there was no improvement in quality of life. Debruyne et al. (2021) enrolled 19 patients with sinus pauses >3 s during Holter or implantable loop recorder. Basal heart rate increased by 18% and remained stable between 6 and 12 months. The treatment was considered to have failed in three patients. Of these three patients, two were ≥70 years of age. Thus, GP ablation for vagally mediated sinus bradycardia should be limited to patients younger than 50 years.

Aksu, Gopinathannair, Bozyel et al. (2021) performed GP ablation in 31 of 241 consecutive patients presenting with symptomatic AVB. They had experienced at least one syncopal episode, and daytime second- or third-degree AVB had been documented. The primary endpoint was freedom from any second- or third-degree AVB on Holter monitoring. Over a mean follow-up of 19.3 ± 15 months, AVB episodes were observed in two (6.7%) of 30 cases, and three (9.6%) patients required pacemaker implantation during follow-up.

Even if the severity of symptoms in most patients affected by vagally mediated sinus bradycardia and/or AVB is modest and does not require any therapy, randomized trials specifically limited to these patients are warranted before GP ablation can be recommended for this subset of patients. Until such studies are available, the procedure should be considered investigational and limited to patients enrolled in formal clinical trials.

Targeting the ligament of Marshall for atrial fibrillation.

In the anatomical–physiological hierarchy of autonomic control of the heart, the intrinsic cardiac nerves (ICN) – organized in macroscopically recognizable ganglionated plexi (GP) and ligament (LOM) and vein (VOM) of Marshall – are not only necessary relay stations from central influences, but are able to activate independently. Whether in response to central control or as a result of local activation, the ICNs are the final implementers of

the autonomic – and potentially pro-fibrillatory – influences on the atrial myocardium. Simultaneous activation of both parasympathetic and sympathetic limbs of the ICNs can lead to paroxysmal AF (Tan et al., 2008) by shortening the action potential and increasing intracellular calcium, respectively (Patterson et al., 2006). Experimentally, ablation of the ICNs can protect against AF (Chiou et al., 1997; Lemola et al., 2008; Schauerte et al., 2000). Thus, the ICNs are a logical target in the treatment of AF. However, clinical approaches to *selectively* ablate ICNs are limited.

The LOM was described in 1850 (Marshall, 1850). The VOM is the normal involution of the left anterior cardinal vein as the venous system transitions from bilateral symmetry to right-dominance, turning the left superior vena cava into the LOM. The VOM is not simply a continuation of the LOM, it also: (1) contains abundant innervation of the ICNs (see below), both parasympathetic (Ulphani et al., 2007) and sympathetic (Kim et al., 2000); (2) functions as a true atrial vein, collecting venous return from atrial tissues; (3) contains a myocardial bundle connected to underlying myocardium (Chou et al., 2003; Kim et al., 2000); and (4) more practically for the clinician, can be retrogradely accessed from the coronary sinus, which is routinely cannulated during ablation procedures.

Functionally and anatomically, the VOM contains both sympathetic and parasympathetic arrhythmia mechanisms. In seminal studies, Scherlag et al. (1972) showed that stimulation of left cardiac sympathetic nerves generated an ectopic atrial rhythm arising from the LOM/VOM area, demonstrating its arrhythmogenic potential of neurogenic origin. A localized increased sensitivity to catecholamines suggested a role in adrenergic atrial tachycardia (Doshi et al., 1999), as supported by abundant sympathetic innervation shown by tyrosine hydroxylase staining (Kim et al., 2000). Staining for acetylcholinesterase also demonstrated abundant parasympathetic innervation in the LOM–VOM area (Ulphani et al., 2007), which had functional relevance since LOM ablation eliminated vagal stimulation-induced decreases in effective refractory period (Ulphani et al., 2007).

Targeting the LOM as part of the GPs has been traditionally performed surgically. A percutaneous approach using ethanol infusion in the VOM showed that regional parasympathetic denervation followed (Valderrabano et al., 2009). VOM ethanol inject abolished the local decrease in effective refractory period created by cervical vagal stimulation, reproducing the effects Ulphani et al. (2007) had demonstrated by ablating the LOM in open-chest models.

The procedure was validated in humans: high-frequency stimulation in the VOM could trigger AF and AV nodal conduction slowing, demonstrating a GP-to-GP communication between VOM-GP and the right inferior GP (which controls the AV node). Such a response was eliminated after VOM ethanol infusion (Baez-Escudero et al., 2014).

While these results provided a clinical validation of procedural feasibility of targeting nerve components by VOM ethanol injection, proving clinical outcome differences required a clinical trial. A multi-centre clinical trial tested the impact of VOM ethanol infusion when added with catheter ablation (CA) in the treatment of persistent AF ablation. The VENUS-AF (Vein of Marshall EthaNol in Untreated perSistent AF) trial (Valderrabano et al., 2019,

2020; NCT 01898221) showed that the proportion of patients with freedom from AF/AT after a single procedure was 49.2% (91/185) in the VOM-CA group compared with 38% (60/158) in the CA group ($P = 0.04$). The procedure had the added benefit of facilitating mitral isthmus ablation, critical for the prevention of perimitral flutter (Baez-Escudero et al., 2012; Lador et al., 2021).

Thus, targeting the ICN via VOM ethanol injection has proven to be beneficial in the clinical treatment of AF. Further studies are needed to confirm the widespread utility of this procedure. Furthermore, the VOM retrograde infusion procedure has opened the door to delivering pharmacological or biological therapies targeting the ICN beyond the crude destruction of ethanol.

Glia and S100B in atrial fibrillation ablation and actions on atrial electrophysiology.

Half a century after initial demonstration of the nature of glial cells in the heart, the presence of a distinct morphological and functional system is now becoming apparent (Allen & Lyons, 2018; Thaemert, 1969).

Glial cells are well known to accompany autonomic nerves and neurons within cardiac ganglia. This is important since glia in the CNS – where they make up more than half of the cells – and the peripheral nervous system are an essential cell type for neuronal functions (Allen & Barres, 2009). Neural control of the heart is concerted by extracardiac and intracardiac glia, which consist of several cell populations that contribute to the modulation of cardiac function (Truter et al., 2023).

Satellite glia in the stellate ganglia, for example, have been found to modulate heart rate and dynamically adapt to changes in neuronal requirements (van Weperen et al., 2021). Cardiac glia have been found to react as a first responder to nerve damage with secretion of the neurotrophic damage-associated pattern response protein S100B (Scherschel et al., 2019). Translational studies suggest that the release of S100B from cardiac glia upon catheter-ablation is a hallmark of acute neural damage that impacts atrial electrophysiology and contributes to nerve sprouting (Scherschel et al., 2019). In particular, S100B can be taken up by intracardiac neurons, most likely via the receptor of advanced glycosylation end products (RAGE), and has the potential to reduce their electrical activity (Scherschel et al., 2019).

Following these initial findings S100 has been used (by applying different methods of measurements) as a blood-based biomarker in several studies to assess intracardiac neural tissue damage in patients undergoing interventional treatment of AF (Guo et al., 2023; Lemoine et al., 2023; Scherschel et al., 2020; Tohoku et al., 2023). Different techniques including radiofrequency, cryo- and pulsed-field ablation have been found to go along with the release of S100 and result in accidental neural tissue damage upon pulmonary vein isolation, now the cornerstone of treatment for patients with AF. In a proof-of-principle study, S100B was released to a lesser extent after pulsed-field ablation compared to thermal ablation (Lemoine et al., 2023). This finding was accompanied with the absence of a relevant increase in heart rate (during sinus rhythm), which is well known to appear after thermal ablation (with about 10 bpm) following accidental partial atrial denervation in

patients with a history of AF. Of interest, these findings have been confirmed by another study, but vagal responses during pulsed field ablation were not associated with the release of S100 (Tohoku et al., 2023).

It is noteworthy that the S100 protein family consists of more than 20 calcium-binding proteins, each with unique characteristics and specific intra- and extracellular functions. Among these, S100B is one of the best characterized. It is abundantly expressed in glial cells and some neuronal populations in the central and peripheral nervous systems and therefore appears to be a useful surrogate parameter for neuronal tissue damage (Truter et al., 2023). However, its presence in the heart might change over time, especially in structural heart disease or following MI (Mohammadzadeh et al., 2013). This needs to be considered when studying cardiac neuromodulation in different settings and patient populations (e.g. including accidental and targeted cardioneuroablation). Also, it is not known whether, how and to what extent glia, acutely and during follow-up contribute to the operation and adaptation of neural circuitry regulating heart rate and rhythm. Novel technologies which are currently under development for selective cardiac neuromodulation might be helpful in this context.

Questions and controversies

- How do age-related changes in cardiac glia impact cardiac morphology, rhythm and function across the human lifespan in health and disease?
- To what extent do cardiac glia impact cardiac neuromodulation and related changes in heart rate and rhythm?
- Can cardiac glial markers be used to monitor targeted cardiac neuromodulation?
- Might cardiac glia be a potential therapeutic target for cardiac neuromodulation?

Gene therapy for autonomic nerves.

Recent years have seen the development of new, gene-based strategies to target autonomic remodelling in the heart, and more specifically in the atria. These strategies have attempted to target both autonomic nerve growth (sprouting) and function of existing autonomic nerves.

Gussak et al. (2019) demonstrated that parasympathetic nerve sprouting may be the cornerstone of autonomic remodelling in the setting of electrical remodelling in AF. That study showed a significant increase in parasympathetic and sympathetic nerve sprouting in a canine model of rapid atrial pacing (RAP)-induced AF. Interestingly, parasympathetic nerve fibres were more inhomogeneously distributed in remodelled atria and thought to contribute to heterogeneous electrical remodelling in the posterior left atrium. Not unexpectedly, this increase in nerve sprouting was accompanied by increase in NGF expression in the left atrium. Surprisingly, NGF elevation in the remodelling left atrium was greater in the left atrial appendage than in the rest of the left atrium. The authors postulated that a more homogeneous pattern of parasympathetic innervation in the left atrial appendage led to more ‘regular’ electrical activation of cardiomyocytes in the appendage, as compared to myocytes elsewhere in the left atrium (posterior left atrium, left atrial free wall). The authors went

on to postulate that NGF released by fibrillating atrial myocytes is retrogradely transported to neuronal cell bodies in the ganglionated plexi and stellate ganglia, thereby leading to hypertrophy of both parasympathetic and sympathetic nerve cell bodies; this hypertrophy of neuronal cells in turn was accompanied by a significant increase in nerve fibre sprouting in all regions of the left atrium.

Building on this work, this group of investigators has attempted to target NGF signalling in the atria using a gene-based approach. Using a small hairpin RNA (shRNA) to NGF, our group at Northwestern targeted NGF signalling in the entire left atrium as well as in a more targeted fashion in the left atrial appendage (unpublished data; presented in abstract form at American Heart Association scientific sessions 2022 and Heart Rhythm Society scientific sessions 2023). Following injection of shRNA in either the entire left atrium or the left atrial appendage, dogs were subjected to RAP for a period of several weeks. As compared to controls, dogs receiving shRNA developed significantly less AF – as measured by the incidence and the duration of AF. This decrease in AF was at least partially a result of longer effective refractory periods in NGF shRNA dogs as compared to controls. Nerve analysis revealed a significant decrease in RAP-induced hypertrophy of neuronal cells in the ganglionated plexi (parasympathetic neurons) and stellate ganglia (sympathetic neurons); this was accompanied by a significant decrease in new nerve sprouting in entire left atrium, including the posterior left atrium and left atrial free wall. Interestingly, NGF shRNA injection in the left atrial appendage alone was as effective as NGF shRNA injection in the entire left atrium. This highlights the important role of the left atrial appendage in modulating neural remodelling in the setting of RAP induced AF.

Since AF is a multifactorial disease, more recently this group of investigators has attempted to target parasympathetic signalling together with oxidative injury, another mechanism underlying AF. Using a combination of NOX2 shRNA (to target NADPH oxidase 2 (NOX2), a major enzymatic source of reactive oxygen species) and $G\alpha_{i/o}$-ct, Mikhailov et al. showed that electrical remodelling in the atria in a canine model could be both prevented and reversed (Mikhailov et al., AHA Scientific Sessions 2022; Mikhailov et al., HRS Scientific Sessions 2023).

Taken together, targeting the ANS – whether by preventing new parasympathetic and sympathetic nerve growth by using a gene-based approach targeting NGF, or whether by using novel minigenes that inhibit parasympathetic (M2-$G\alpha_{i/o}$) signalling in the atria – appears to be able to not only prevent but also potentially reverse electrical remodelling in the setting of persistent AF. Further refinement of these gene-based approaches may lead to the development of new, mechanism-guided therapies for AF.

Renal denervation and splanchnic neuromodulation.

The foundational insights into the neural control of kidney function date back to 1859, with observations that cutting the greater splanchnic nerve (GSN) led to increased urine output on the same side. Conversely, electrically stimulating the cut nerve’s end produced the reverse effect, indicating that removing the influence of renal sympathetic nerves enhanced diuresis, whereas their stimulation reduced urine output (DiBona & Esler, 2010). This principle was further demonstrated in studies of kidney blood flow, showing that nerve removal boosted

blood flow, while electrical stimulation of the nerve reduced it (Starling, 1908). Research measuring activity in renal sympathetic nerves revealed that enhancing this activity through electrical stimulation increased the secretion of renin and the reabsorption of sodium, and caused renal vasoconstriction (DiBona & Kopp, 1997).

The adrenergic nerves that supply the kidneys, running along the renal artery to the smaller blood vessels and juxtaglomerular apparatus, thus become a potential point of intervention to enhance blood flow, reduce renin production, minimize vasoconstriction and decrease sodium reabsorption (Barajas, 1964; Barajas & Muller, 1973). This approach is particularly relevant in the context of hypertension, where these normal mechanisms are believed to be disrupted. Elevated renal sympathetic nerve activity has been identified in individuals with essential hypertension, especially those resistant to treatment (DiBona & Esler, 2010; Esler, 2014). Afferent nerve fibres, which relay both mechanical and chemical signals to the brain using various neurotransmitters, play a role in both stimulating and dampening responses that affect urine production and sodium balance (Kopp et al., 1985; Liu & Barajas, 1993; Stella & Zanchetti, 1991; Ye et al., 2002). Techniques like the removal of both kidneys, which eliminates the source of afferent signals to the CNS, and dorsal rhizotomy, the surgical removal of specific dorsal roots, have been shown to reduce high blood pressure (Campese & Kogosov, 1995; Converse et al., 1992). Such interventions have demonstrated significant blood pressure reduction in humans with end-stage renal disease on dialysis and high blood pressure, and in rat models of hypertension, indicating the potential effectiveness of targeting these neural pathways in managing hypertension (Campese & Kogosov, 1995; Converse et al., 1992).

These findings and others provided strong rationale for renal denervation (of both afferent and efferent nerves) in humans to treat hypertension. Percutaneous renal denervation is one of the few approved neuromodulation technologies for the management of cardiovascular disease. This therapy applies radiofrequency or ultrasonic waves from an endoluminal catheter, through the walls of both renal arteries to ablate nerves running along the vessel wall. The two technologies with the most clinical data and approval for clinical use in the US and abroad are the Spyral catheter (Medtronic, Minneapolis, MN, USA) and Paradise system (ReCor Medical, Menlo Park, CA, USA). The journey to approval was complex, starting with initial promising outcomes from the Simplicity HTN-1 and -2 trials (Esler et al., 2010; Krum et al., 2009), which were not replicated in the larger Simplicity HTN-3 trial (Bhatt et al., 2014). This led to the development of the SPYRAL OFF-MED and ON-MED trials to rectify issues related to trial designs, operator expertise and device functionality. The SPYRAL OFF-MED trial, a global, multicentre, single-blind study, introduced significant changes in patient selection, catheter technology and treatment protocols compared to simplicity HTN-3 (Townsend et al., 2017). It specifically excluded patients with isolated systolic hypertension, who show less responsiveness to renal denervation (RDN), and introduced a new multi-electrode catheter with an improved ablation technique aimed at a more thorough and effective renal denervation by targeting a wider and more varied selection of ablation sites (Mahfoud et al., 2015, 2017).

In the SPYRAL OFF-MED Pivotal trial, 331 patients were randomly assigned to undergo either RDN or a placebo procedure (Böhm et al., 2020). The trial’s main

goalsweretoassesschangesin24-hsystolicbloodpressure (SBP) and office SBP, adjusted from baseline, at a 3-month follow-up. Results showed a significant advantage for RDN, with a reduction in 24-h SBP by an average of 3.9 mmHg and in office SBP by 6.5 mmHg, without any major safety concerns related to the device or procedure. These outcomes strongly support the effectiveness of RDN in controlling blood pressure in humans (Böhm et al., 2020). Meanwhile, the SPYRAL ON-MED trial observed a smaller average reduction in 24-h ambulatory systolic BP between the RDN group and the sham control group, showing a difference of 1.9 mmHg, which was not statistically significant (Kandzari et al., 2023). However, the trial did note a substantial decrease in office SBP in the RDN group compared to the sham group at the 6-month mark, alongside improvements in night-time blood pressure, suggesting benefits of RDN under certain conditions.

A competitor ultrasound based RDN technology (ReCor Medical) was also proven to be effective and safe in a series of clinical trials. The RADIANCE-HTN study (NCT02649426) evaluated the effectiveness of the ReCor Medical Paradise ultrasound system against a placebo in lowering daytime ambulatory SBP over a 2-month period post-treatment, within two distinct patient groups with uncontrolled hypertension: those on medication (TRIO) and those not on medication (SOLO) (Mauri et al., 2018). In the TRIO group, 989 individuals with resistant hypertension were taken off their existing medications and placed on a uniform regimen of a single pill combining a calcium channel blocker, an angiotensin receptor blocker and a thiazide diuretic (Azizi et al., 2021). Of these, 136 patients meeting specific blood pressure criteria were then randomized to receive either the ultrasound-based RDN or a placebo. The RDN group experienced a median drop in daytime SBP significantly greater than the placebo group, by 4.5 mmHg, without any notable difference in safety outcomes (Azizi et al., 2021). The SOLO group consisted of 146 patients who, after stopping up to two blood pressure medications for 4 weeks, underwent randomization to the same treatments (Azizi et al., 2018). Results for the SOLO group similarly favoured RDN, showing a more substantial decrease in daytime SBP than the placebo, with a difference of 6.3 mmHg between the groups and no significant adverse events.

These findings reinforce the potential of renal sympathetic nerve modulation not just in managing hypertension but also in its broader implications for treating other conditions such as heart failure, AF and cardiometabolic syndrome, indicating that the influence of renal sympathetic nerves extends well beyond regulating blood pressure alone.

Modulating the GSN represents another promising autonomic approach to treating heart failure. The splanchnic blood vessels, which contain up to 30% of the body’s total blood volume, and are densely innervated by sympathetic nerves, play a crucial role in regulating blood volume distribution (Fudim, Sobotka et al., 2021). Normally, these vessels help increase cardiac preload – a necessary adjustment during increased cardiac output demands, such as during exercise – by shifting blood from the splanchnic region to the heart and lungs (Burkhoff & Tyberg, 1993; Fallick et al., 2011; Fudim et al., 2017; Sorimachi et al., 2021). However, in individuals with diminished venous capacity, this shift can lead to harmful increases in lung and central heart pressures. Attempts to disrupt splanchnic nerve communication in small, preliminary studies have explored techniques like temporary nerve blocking or surgical removal of the right-sided GSN. These interventions, particularly in

cases of acute decompensated heart failure (Fudim, Ganesh et al., 2018; Fudim, Jones et al., 2018) and chronic heart failure (Fudim, Boortz-Marx et al., 2020; Fudim et al., 2023), have been observed to lower cardiac filling pressures, likely due to enhanced vasodilatation and resulting in decreased blood volume under stress (Fudim, Ganesh et al., 2018; Fudim, Jones et al., 2018; Fudim, Boortz-Marx et al., 2020; Fudim, Patel et al., 2021; Fudim et al., 2022a; Fudim et al., 2023). Notably, the effectiveness of these interventions seemed to increase with the extent of nerve blockade, with more complete blocking leading to a more significant reduction in preload, sometimes even resulting in temporary orthostatic hypotension (Fudim, Boortz-Marx et al., 2020). Encouraged by these initial findings, research has progressed to developing a catheter-based endovascular procedure aimed at ablating the right-sided GSN for managing heart failure with preserved ejection fraction (HFpEF). This novel treatment, known as splanchnic ablation for volume management (SAVM) (Fudim, Engelman et al., 2022), has demonstrated positive safety outcomes in early trials, showing potential as a therapeutic option (Fudim, Fail et al., 2022).

The REBALANCE-HF phase II feasibility trial (NCT04592445) was designed to test the hypothesis that endovascular ablation of the right-sided GSN (the so called SAVM procedure) in patients with symptomatic HFpEF and documented invasive exercise pulmonary capillary wedge pressure (PCWP) of at least 25 mmHg reduces legs up- and exercise PCWP compared to sham control (Fudim, Engelman et al., 2022; Shah et al., 2024b). In a group of patients with HFpEF, the study demonstrated that the procedure is safe with high probability of procedural success, but there was no difference in the primary efficacy endpoint between SAVM and sham (Shah et al., 2024a). However, responder analyses provide insights into HFpEF phenotypes in whom SAVM may be beneficial, which will be tested in a prospective trial.

Questions and controversies

- Who are the ideal patients for renal and splanchnic denervation?
- What are the optimal measures of technical and therapeutic success after renal and splanchnic denervation?
- What other diseases might benefit from renal and splanchnic denervation?
- Will renal denervation, when combined with other organ denervation procedures, be of additive benefit?
- How do we practically identify patients with inappropriate central blood shifts and likely associated sympathetic overdrive that may benefit from splanchnic nerve ablation?

Baroreflex activation therapy.

The imbalance between sympathetic and parasympathetic activity is a known predictor of poor outcomes and symptoms in patients with HFrEF. Baroreflex activation therapy (BAT), administered by a device similar to a pacemaker known as the Barostim neo system (CVRx, Inc., Minneapolis, MN, USA), offers electrical stimulation to the carotid sinus. This aims to suppress the activation of the sympathetic nervous system while enhancing the effects of the

parasympathetic nervous system. The device, implanted below the collarbone and connected to a small electrode placed directly on the carotid sinus, activates baroreceptors to reduce sympathetic and increase parasympathetic activity (Abraham et al., 2015; Georgakopoulos et al., 2011; Gronda et al., 2014).

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The BeAT-HF trial, a prospective, multicentre, randomized, controlled study, divided 408 HFrEF patients into two groups: those receiving BAT alongside optimal medical management and those receiving only optimal medical management. Patients were eligible if they were in the NYHA functional class III or class II with recent class III history, had an ejection fraction of 35% or less, were on stable medical management for 4 weeks or more, and did not require cardiac resynchronization therapy (CRT) (Zile et al., 2020).

Out of four patient cohorts, one specifically met the US Food and Drug Administration (FDA)-approved criteria for BAT use, involving 245 patients monitored over 6 months. BAT was found to be safe, with a high rate of being free from major adverse neurological, cardiovascular or procedure-related events. In comparison to the control group, the BAT group showed improvements in quality-of-life scores, increased 6-min walk distances and reduced N-terminal (NT)-proBNP levels (Zile et al., 2020).

Following the BeAT-HF study’s results, in 2019, the FDA approved the Barostim Neo device for improving heart failure symptoms, quality of life, walking ability and functional status in symptomatic patients (NYHA III or class II with a recent history of class III) who are already on guideline-directed medical therapy (GDMT), have an LVEF of 35% or less and an NT-proBNP level below 1600 pg/ml, excluding those indicated for CRT. This marked the first FDA approval of a neuromodulation technology for HFrEF. The FDA has mandated the continuation of the BeAT-HF study to further investigate the effects on mortality and heart failure hospitalizations.

The extended study results showed no significant difference in cardiovascular mortality and heart failure morbidity between the BAT and control groups (Zile, 2023). However, a prespecified win ratio analysis highlighted the benefits of BAT across several outcomes, including cardiovascular mortality, LVAD/heart transplant, heart failure hospitalizations and quality of life. For an additional BAT-based examination, Coats et al. performed an individual patient data meta-analysis on the two trials that randomized 545 HFrEF patients

to BAT and GDMT or GDMT alone (open label) (Coats et al., 2022). The 2022 AHA/ACC/HFSA and 2021 ESC guidelines acknowledge the modest improvements in effort capacity and quality of life offered by ANS modulation technologies like BAT (Heidenreich et al., 2022; McDonagh et al., 2021).

Efforts to increase BAT adoption include a less invasive interventional implantation technique under investigation, which uses a BAT wire implant kit and ultrasound guidance for placing the stimulation lead near the carotid baroreceptors, with a study enrolling 100 subjects across up to 35 US sites.

Additionally, endovascular mechanical baroreceptor amplification, such as the MobiusHD system (vascular dynamics), represents another method of BAT, utilizing mechanical stretching of the carotid sinus to activate it. Though primarily showing efficacy in resistant hypertension, limited data indicate potential benefits in HFrEF treatment, with significant improvements observed over a 12-month period in a small study, prompting further investigation through the ongoing HF-FIM trial (Spiering et al., 2017). These developments illustrate the evolving field of heart failure treatment, exploring both electrical and mechanical means of baroreflex activation.

Transcranial magnetic stimulation.

Non-invasive methods to stimulate the brain remain an area of significant research interest and clinic intervention. To this end, brain stimulation achieved by means of a magnetic field generated by passing current through primary and secondary coils positioned to activate specific brain regions is rapidly gaining popularity (Bakker et al., 2015). Transcranial magnetic stimulation (TMS) has received FDA approval for conditions such as treatment-resistant depression, obsessive–compulsive disorder and migraine headaches.

Autonomic neuromodulation using TMS is poorly understood, but it has shown significant promise for patients with severe ventricular arrhythmias. In a landmark study (Markman et al., 2022), 26 patients with electrical storm were enrolled in a double blind sham-controlled randomized clinical trial of TMS targeting the stellate ganglion. In the 72 h following randomization to TMS, patients experienced a reduction in VT episodes from 10.7 ± 13.8 to 4.5 ± 7.2 ($P < 0.001$). This reduction was associated with a reduction in the number of antiarrhythmic medications 24 h following randomization to TMS but not in the sham group. These promising findings are yet to be validated in larger studies, while questions such as safety of TMS in the presence of implanted cardiac electrical devices (Wegner et al., 2024), mechanisms of action, dosing and targeted brain areas remain unanswered.

Sleep apnoea interventions.

The treatment of OSA is evolving based upon our understanding of the benefits of individualized targeting of underlying contribution of endotypes which include anatomical compromise, ventilatory control instability (loop gain), arousal threshold and impaired pharyngeal dilator muscle function. Although the frequency measure of respiratory events, that is, the apnoea–hypopnoea index, has been considered the traditional measure to define sleep apnoea, the prognostic value of other measures including sleep apnoea-specific hypoxic burden and heart rate arousal response is becoming increasingly recognized

(Malhotra et al., 2021). These measures hold promise in better characterization of specific aspects of OSA pathophysiology, e.g. heart rate arousal response serving as a specific physiological biomarker of sleep apnoea-related autonomic influence, and also perhaps represent helpful targets to assess treatment responsiveness.

Positive airway pressure (PAP) either via nasal or oronasal interface applied to the upper airway, serves as a pneumatic splint, thereby alleviating airway obstruction, and is considered to be the mainstay of treatment for OSA. In central sleep apnoea, PAP therapy operates to stabilize breathing and most often results in effective control. There is strong evidence that PAP therapy in OSA results in reduced blood pressure profiles with benefits most pronounced in resistant hypertension. PAP therapy also results in improvement of surrogate ANS parameters of HRV with these improvements most pronounced at night, in men and in those with arterial hypertension (Friscic et al., 2023).

Neurostimulation therapies have also emerged as treatments for both obstructive and central sleep disordered breathing. Hypoglossal nerve stimulation (HNS) improves OSA burden, particularly in those who are less obese older age and seemingly in women (Heiser et al., 2019). HNS results in improvement in patient reported outcomes, including dozing propensity, functional outcomes related to sleep, depression and insomnia (Pascoe et al., 2022; Strollo et al., 2014). Initial interventional trial data do not support benefit of HNS on 24-h systolic blood pressure profiles (Dedhia et al., 2024; Walia et al., 2020). Whether this is attributable to study design limitations, including lack of inclusion of those most likely to derive blood pressure improvement, or whether it is indeed indicative of true lack of benefit perhaps due to neurostimulation-induced background sympathetic hyper-reactivity remains unknown. Phrenic nerve stimulation results in lower apnoea–hypopnoea index and central apnoea burden as well as arousal index and possible improvements in sleepiness and degree of hypoxia. The long-term influence of these neurostimulation interventions on cardiovascular outcomes and impact on ANS pathophysiology remains unclear.

In summary, a breadth of neuromodulation strategies exist for patients with (Fig. 9) or without structural heart disease. For patients with VAs, recent guidelines on clinical management now include autonomic modulation as a Class IIb indication (Al-Khatib et al., 2018).

Meditation, holistic interventions and aerobic exercise.

Holistic interventions, encompassing psychological, social and spiritual facets of health, are becoming integral to modern healthcare. These complementary and integrative approaches are increasingly adopted alongside conventional medicine, with substantial out-of-pocket investments highlighting their societal value (Barnes et al., 2004; Black et al., 2015). Recent data show a continuing trend in the utilization of practices such as meditation, yoga, psychotherapy, exercise and dietary modification, reflecting a strengthening of the shift towards the inclusion of mind–body medicine in healthcare (Carlson et al., 2017; Clarke et al., 2018; Fjaer et al., 2020). Healthcare systems are responding by incorporating these approaches, as evidenced in comprehensive care models for chronic illnesses like cancer (Bultz et al., 2014; Deng, 2019). The popularity of such interventions necessitates rigorous evaluation of their efficacy, safety and mechanisms of action, and has led to prominent

consideration of their inclusion within the context of cardiovascular care (Levine et al., 2021).

Stress has a well-documented influence on cardiovascular health, with both physical and mental stressors contributing to the onset and progression of heart disease (Golbidi et al., 2015; Nemeroff & Goldschmidt-Clermont, 2012; Thurston et al., 2013). Early research highlighted the link between acute mental stress and increased cardiac risks, including arrhythmias and sudden cardiac death (DeSilva & Lown, 1978; Lown & DeSilva, 1978). Emotions such as anger appear to intensify this risk (Krantz et al., 2021), whereas depression predicts higher post-MI mortality (Sundboll et al., 2017; Worcester et al., 2019). Large-scale studies corroborate these findings, associating significant emotional events with spikes in acute coronary syndromes (Borges et al., 2013; Wilbert-Lampen et al., 2008, 2010). Emotional stress may also unveil existing cardiac conditions or induce acute ventricular dysfunction, such as takotsubo cardiomyopathy, due to heightened sympathetic activity and stress (Medina de Chazal et al., 2018; Templin et al., 2015).

Recent scrutiny in the field of mind–body interventions points to the need for larger, more rigorous studies with randomized and adequately controlled conditions to address potential biases and validate efficacy. Since 2016, there has been a push towards refining trial designs, particularly in distinguishing the specific effects of interventions beyond wait-list controls or care as usual comparators (Dossett et al., 2020). However, to date, only a few studies have incorporated such designs or other forms such as non-inferiority or superiority trials (Hoge et al., 2023; Simon et al., 2021). Holistic interventions for cardiac arrhythmias have continued to be conducted, with findings that point towards beneficial effects of mind–body interventions. Most studies remain small in nature, lack a multi-site framework, and tend to use less stringent comparators (e.g. wait-list controls or usual care groups). For example, a study of mindfulness-based psychotherapy for AF found improvements in health-related quality of life at 12 months relative to treatment as usual (Malm et al., 2018). Two studies observed a positive effect of a yoga augmentation versus care as usual on clinical outcomes and quality of life in patients with recurrent vasovagal syncope (Sharma et al., 2022; Shenthar et al., 2021). Finally, clinical wisdom continues to affirm the role of aerobic exercise in enhancing autonomic regulation across various pathologies, including heart failure, by augmenting cardiac autonomic indices. However, even in this area there remains a limited database of high-quality evidence, for conditions such as AF (Risom et al., 2017) or congenital heart disease (Williams et al., 2020). Given the nascent state of the science on holistic interventions in neurocardiology, and the increasing popularity of such interventions, there are a number of questions and controversies regarding how they are being integrated into standard care.

Questions and controversies

- What specific pathways or physiological processes are targeted by mind–body interventions that can be directly linked to improvements in cardiac arrhythmias?
- How can concerns about the over-commercialization of certain practices, such as exercise or meditation and potential scepticism from the medical community be

balanced against the low risk of recommending interventions to promote positive psychological health?

- How can we determine which patient subgroups will benefit most from certain mind and body interventions in order to personalize these therapies based on patient characteristics or disease specifics?

Conclusions

The ANS exerts powerful control over all aspects of cardiac function and is central to the initiation and progression of several cardiovascular diseases. This simple concept establishes the rationale for neuroscience-based interventions to treat disorders of the heart. However, the promise of neuromodulation cannot be fulfilled without (1) advancing our understanding of complex mechanisms of integrated cardiac physiological control by the nervous system, (2) deepening our appreciation of pathophysiological mechanisms mediating neural remodelling following cardiac injury, (3) identification of proper biomarkers to guide patient selection, neuroscientific intervention and dosing, (4) interventions beyond implanted electrical devices and large clinical trials that establish efficacy, and (5) low cost therapeutic solutions that can be deployed across the globe to benefit the entire human race. The field acknowledges major investments made by the National Institutes of Health Stimulating Peripheral Activity to Relieve Conditions (SPARC) (Health, 2014) and the recently funded Fondacion Leducq Transatlantic Network Award to Professors David Paterson (University of Oxford) and Kalyanam Shivkumar (University of California-Los Angeles) to advance Neurocardiology. Further major efforts are needed to advance the field of Neurocardiology and bring novel neuroscientific-based therapies to the bedside.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Kalyanam Shivkumar received his medical degree from the University of Madras, India, and his PhD from UCLA. He completed his cardiology fellowship at UCLA and is currently a Professor of Medicine and Radiology, as well as the director of the UCLA Cardiac Arrhythmia Center. His specialization is in interventional cardiac electrophysiology and innovative techniques for the non-pharmacological management of cardiac arrhythmias. His research focuses on the mechanisms of cardiac arrhythmias in humans, particularly the role of the autonomic nervous system.

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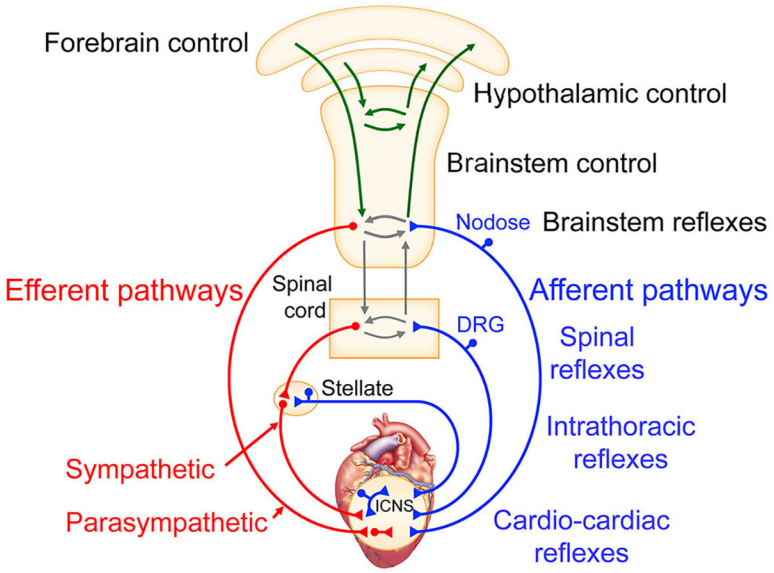

Figure 1. Organization of cardiac neural control

Shown are the ascending nested feedback loops governing cardiac neural control. Afferent information from the heart is relayed to various nodes across the nervous system, while the output from local circuit processing at these sites is relayed as efferent information back to the heart. Figure adapted with permission from Shivkumar et al. (2016), *Journal of Physiology*, *594*(14), 3911–3954.

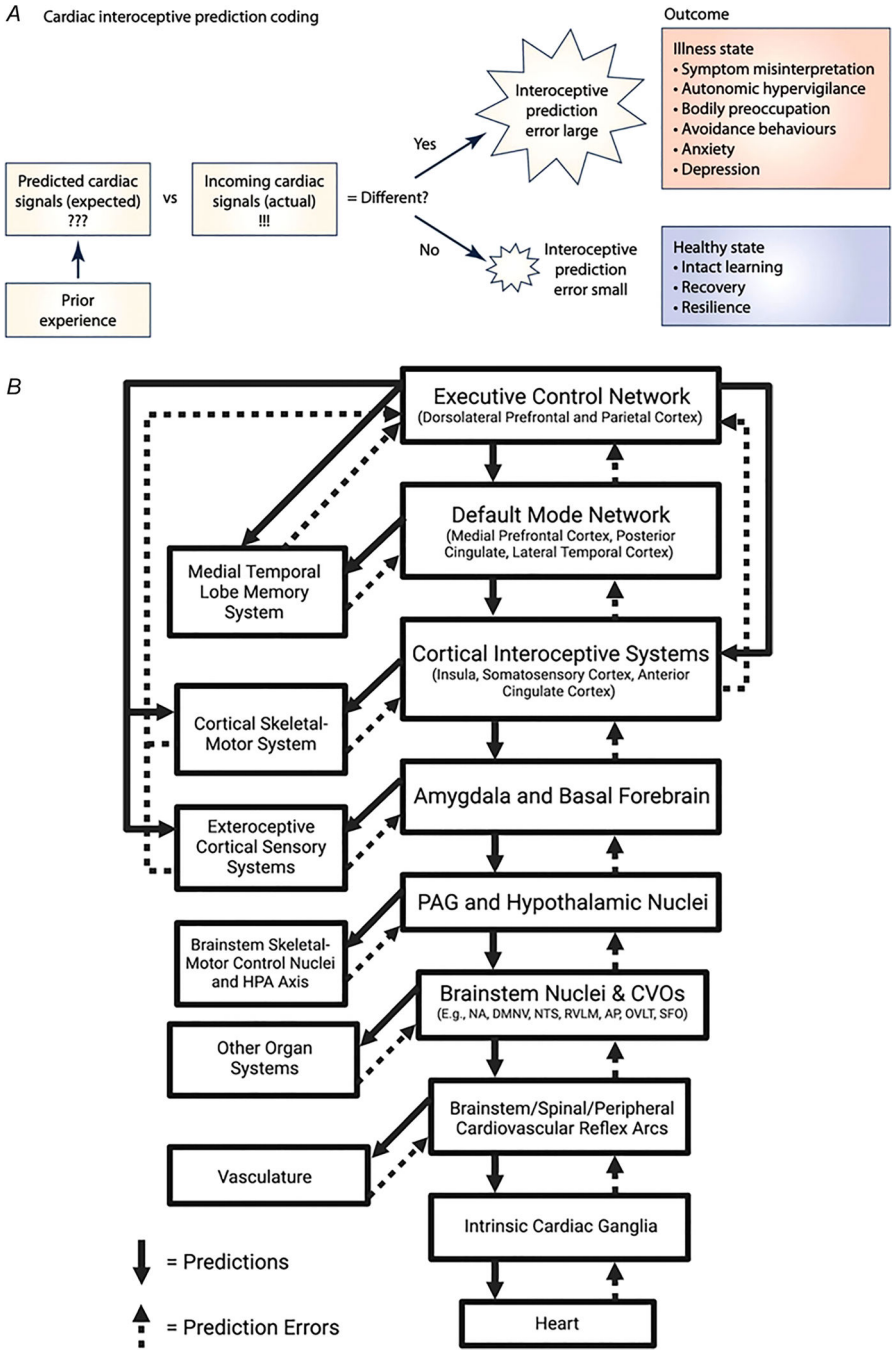

Figure 2. Cardiac interoceptive mechanisms

A, the brain's ongoing comparison between incoming and predicted signals results in calculation of an interoceptive prediction error. Disruptions in cardiovascular homeostasis result in large interoceptive prediction error signals, and this can produce illness states if the system is unable to adequately adapt. *B*, updated model of neurovisceral integration for heart–brain interactions (reproduced, with permission, from Smith et al., 2017). This model illustrates the hierarchical flow of predictions and prediction errors between levels as well as the integration of additional information from other systems that occur at each level.

AP, area postrema; CVO, circumventricular organs; DMNV, dorsal motor nucleus of the vagus; HPA, hypothalamic–pituitary–adrenal; NA, nucleus ambiguous; NTS, nucleus tractus solitarius; OVLT, organum vasculosum of the lamina terminalis; RVLM, rostroventrolateral medulla; SFO, subfornical organ.

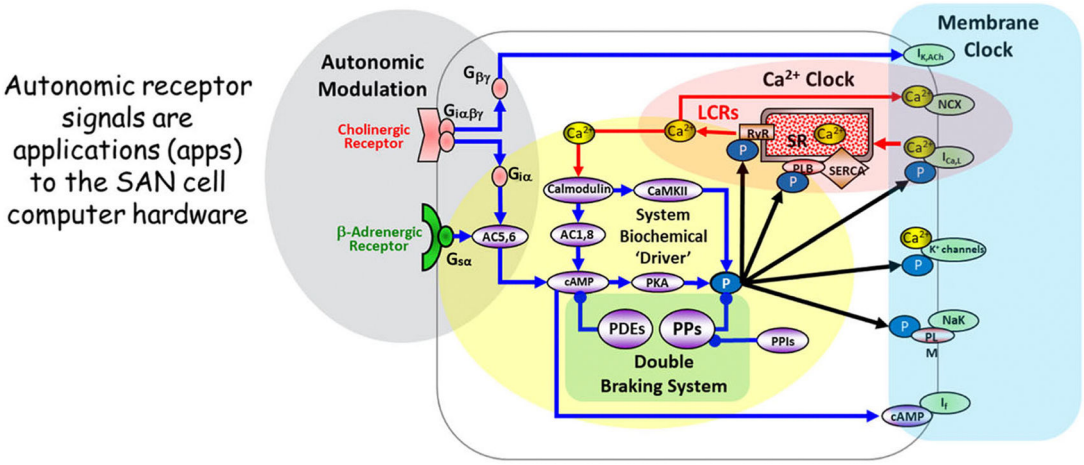

Figure 3. Autonomic modulation of the pacemaker coupled clock system

A schematic representation of the coupled-clock system that generates automaticity of SAN pacemaker cells, see text for details (Sirenko et al., 2021). AC, adenylyl cyclase; CaMKII, Ca^{2+}–calmodulin dependent protein kinase II; cAMP, cyclic adenylyl 3 -monophosphate; CNGC, cyclic nucleotide gated channel; $G_{\beta\gamma}$, G-protein coupled receptor beta, gamma subunits; $G_{i\alpha}$, G-protein coupled receptor inhibitory alpha subunit; $G_{s\alpha}$, G-protein coupled receptor stimulatory alpha subunit; I_{CaL}, L-type Ca^{2+} current; I_f, hyperpolarization-activated current; $I_{K,Ach}$, acetylcholine-activated K^+ current; LCR, local submembrane Ca^{2+} release; NCX, Na^+/ Ca^{2+}exchanger; P, phosphorylation; PDE, phosphodiesterase; PKA, protein kinase A; PLB, phospholamban; PLM, phospholemman; PP, phosphoprotein phosphatase; PPI, phosphoprotein phosphatase inhibitor; RyR, ryanodine receptor; SERCA, SR Ca^{2+}-ATPase; SR, sarcoplasmic reticulum. Other important members of the coupled-clock system, e.g. IP3 receptors, store operated channels and mechano-sensitive ion channels are not shown in the figure. Figure adapted with permission (Sirenko et al., 2021).

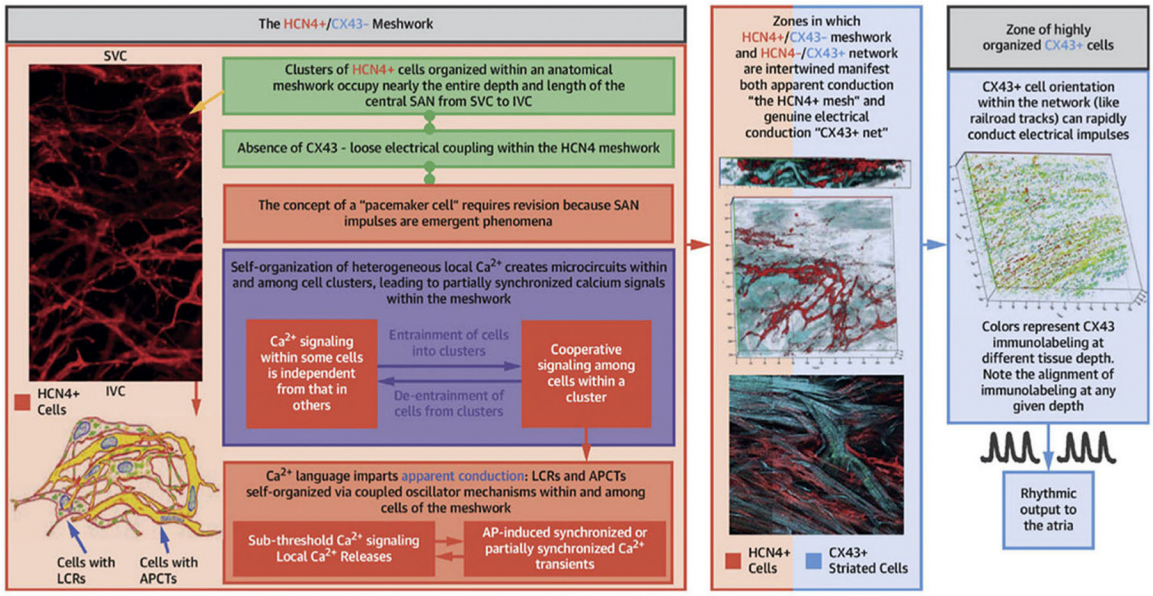

Figure 4. A novel SA nodal structure–function paradigm

A recent discovery has added a new layer of complexity to the initiation of each heartbeat that extends well beyond the coupled-clock system intrinsic to individual SAN cells: the heart's pacemaker cytoarchitecture and function mimics that of the brain. Panels illustrate an HCN4 meshwork (left panel), an intertwining area (central panel), and a CX43 network of cells (right panel). Spontaneous signals are generated within the HCN_4 meshwork and transmitted to the CX43 network of cells through the intertwining area. AP, action potential; APCT, action potential-induced Ca^{2+} transient; CX43, connexin 43: $HCN4^{+}$, hyperpolarization-activated cyclic nucleotide-gated channel 4; IVC, inferior vena cava; LCR, local Ca^{2+} release; SAN, sinoatrial node (from Bychkov et al., 2020 with permission; see also online video 9 from the same paper).

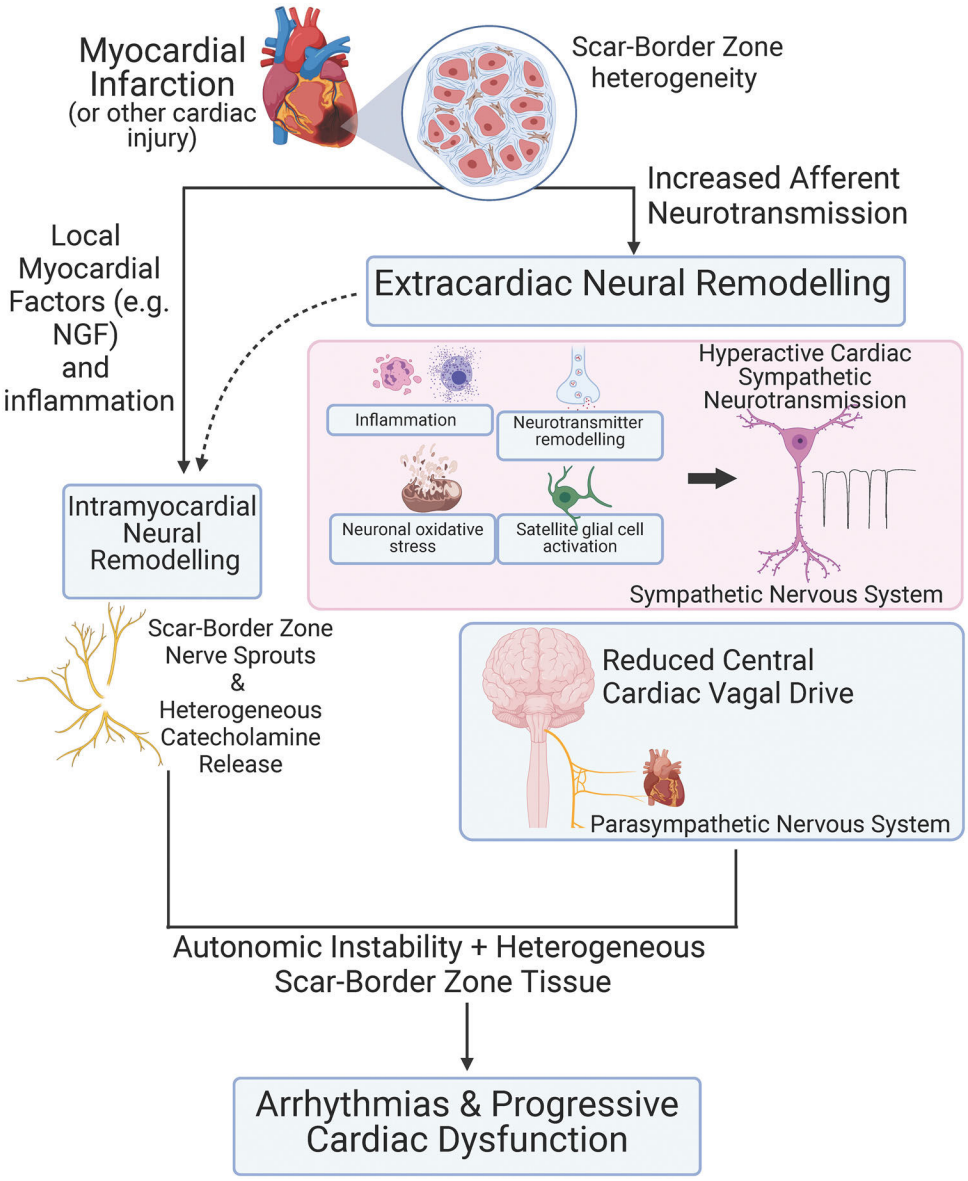

Figure 5. Intra- and extra-cardiac neural remodelling in chronic cardiac injury

Sympathetic and parasympathetic remodelling following chronic myocardial infarction results in sympathetic hyperactivity and parasympathetic withdrawal, which interact maladaptively with chronically injured myocardium to promote arrhythmias and progressive cardiac dysfunction. Figure adapted with permission from Donahue et al. (2024), *Circular Research*, *134*(3), 328–342.

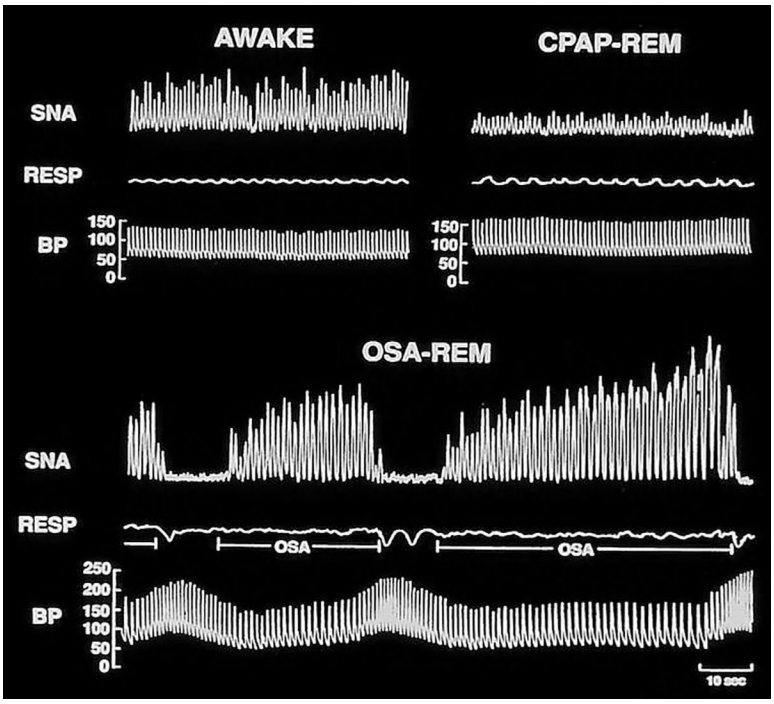

Figure 6. Sympathetic hyperactivity and obstructive sleep apnoea

Sympathetic nerve activity (SNA), respiratory tracings (RESP) and blood pressure (BP) are shown while awake, during rapid eye movement (REM) sleep phase with continuous positive airway pressure (CPAP) use, and during REM sleep with obstructive sleep apnoea (OSA). Sympathetic hyperactivity and hypertension can be readily appreciated during OSA-REM. Figure adapted with permission from Somers et al. (1995), *Journal of Clinical Investigation*, *96*(4), 1897–1904.

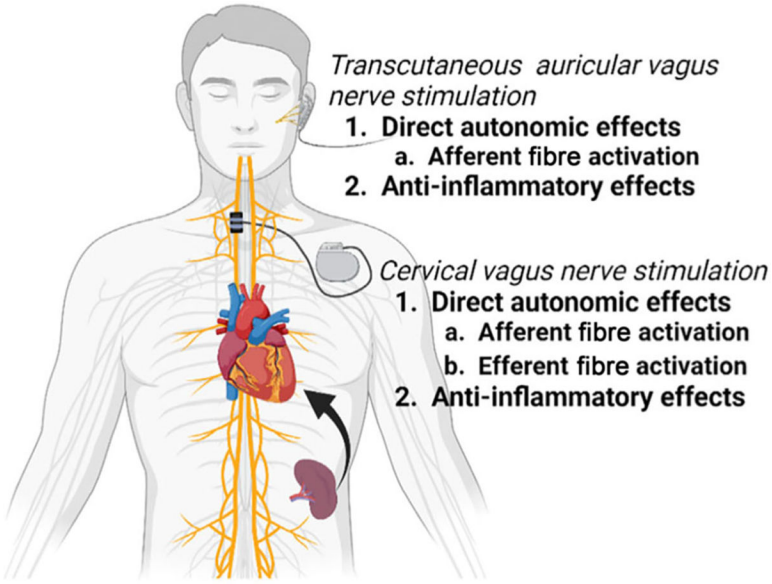

Figure 7. Mechanisms of vagal nerve stimulation and low-level tragus stimulation

Adapted with permission from Zafeiropoulos et al. (2024), *Trends in Cardiovascular Medicine*, S1050–S1738.

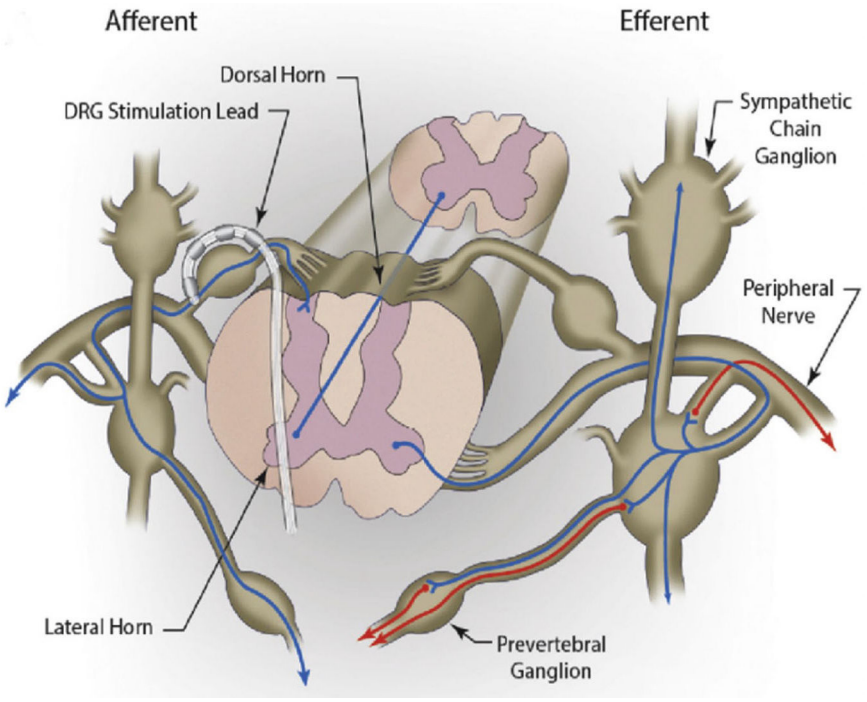

Figure 8. Schematic representation of dorsal root ganglion stimulation.

Depicted is the anatomical relationship of the dorsal root ganglion (DRG) to the sympathetic chain and spinal cord. An implanted lead is illustrated directly over the dorsal DRG. DRG stimulation exerts influences on sympathetic neurons in the spinal afferent pathways, which in turn either influence efferent pathways via the ventral horn at the same segmental level or travel via propriospinal pathways to higher levels to impact blood pressure control. Adapted with permission from Sverrisdottir et al. (2020), *JACC BTS*, *5*(10), 973–985.

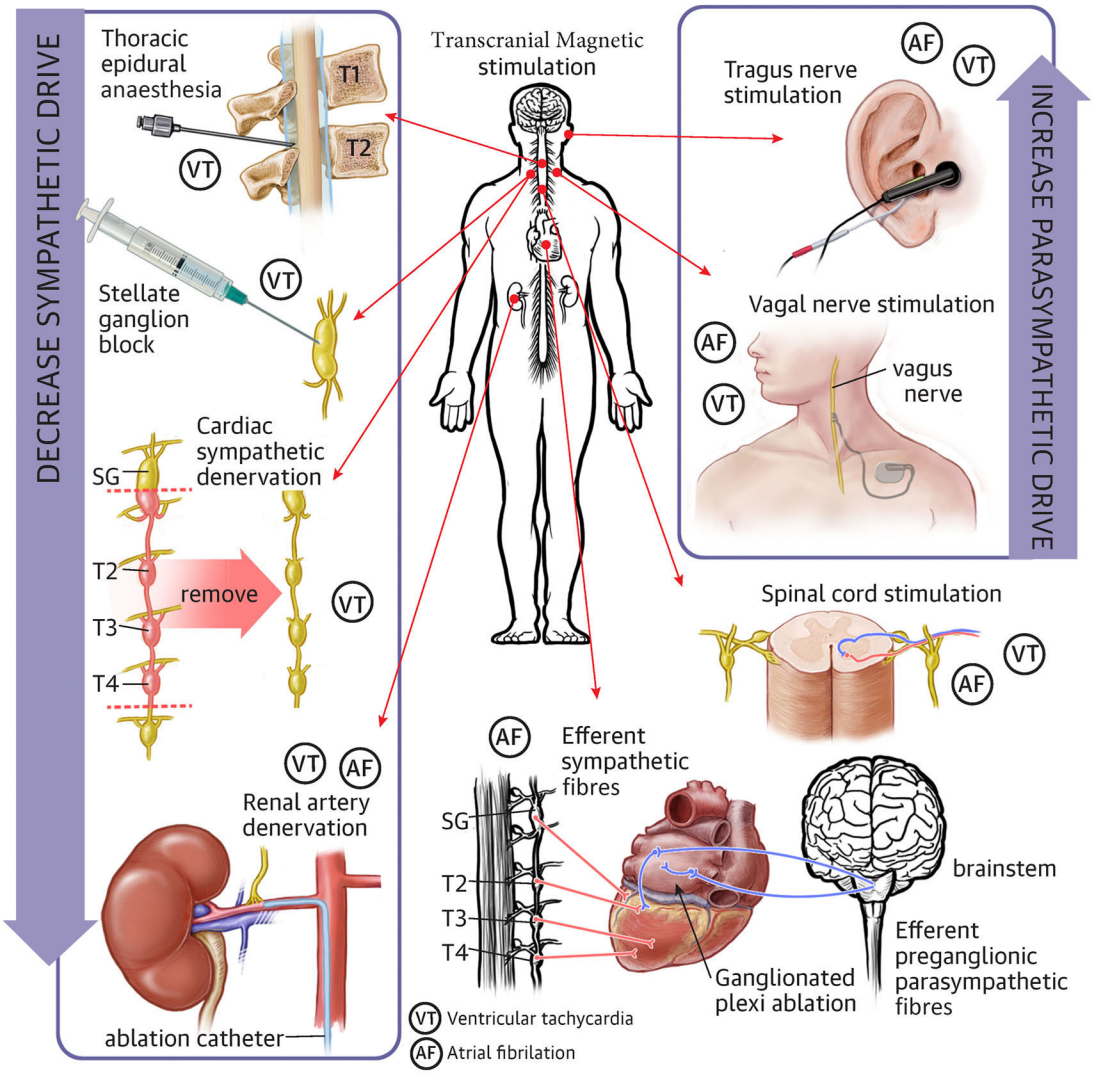

Figure 9. Cardiac neuromodulatory approaches in structural heart disease

A schematic representation of interventions utilized for cardiac neuromodulation against various cardiovascular diseases. Adapted with permission from Zhu et al. (2019), *Journal of American College of Cardiology*, *5*(8), 881–896.

Table 1.

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