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WHITE PAPER

Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics

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Abstract The autonomic nervous system regulates all aspects of normal cardiac function, and is recognized to play a critical role in the pathophysiology of many cardiovascular diseases. As such, the value of neuroscience-based cardiovascular therapeutics is increasingly evident. This White Paper reviews the current state of understanding of human cardiac neuroanatomy, neurophysiology, pathophysiology in specific disease conditions, autonomic testing, risk stratification, and neuromodulatory strategies to mitigate the progression of cardiovascular diseases.

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Abbreviations ABVN, auricular branch of the vagus nerve; AE, adverse event; AF, atrial fibrillation; ANS, autonomic nervous system; ARI, activation recovery interval; ART, autonomic regulation therapy; ASV, adaptive servo-ventilation; AV, atrioventricular; CHF, clinical heart failure; CPVT, catecholaminergic polymorphic ventricular tachycardia; CSA, central sleep apnoea; CSD, cardiac sympathetic denervation; CSR, Cheyne–Stokes respiration; GP, ganglionated plexi; HF, heart failure; HRV, heart rate variability; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; ICN, intrinsic cardiac nervous system; LBNP, lower body negative pressure; LCSD, left cardiac sympathetic denervation; LLTS, low-level tragus stimulation; LL-VNS, low-level vagus nerve stimulation; LOM, ligament of Marshall; LQTS, long QT syndrome; LSG, left stellate ganglion; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSNA, muscle sympathetic nerve activity; NICM, non-ischaemic cardiomyopathy; NGF, nerve growth factor; PV, pulmonary vein; PVI, pulmonary vein isolation; SCD, sudden cardiac death; SG, stellate ganglion; SCS, spinal cord stimulation; TEA, thoracic epidural anaesthesia; OSA, obstructive sleep apnoea; RSNA, renal sympathetic nerve activity; VA, ventricular arrhythmia; VNS, vagus nerve stimulation; VOM, vein of Marshall; VT, ventricular tachycardia.

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As such, although often using some reductionistic models, I do my best to remain a pupil at the school of complexity
Alberto Malliani (1935–2006)

(*Principles of Cardiovascular Neural Regulation in Health and Disease*, pp. xiv–xv, Springer Science + Business Media, LLC, 2000).

Introduction

Understanding cardiac autonomic regulation is a prerequisite to comprehending the development and progression of most cardiovascular diseases (hypertension, heart failure, arrhythmias and myocardial infarction) and cardio-respiratory diseases such as sleep apnoea. Enhanced cardiac sympathetic activity and attenuated parasympathetic central drive are noted in several cardiac disorders, portend poor prognosis, and are associated with arrhythmias and sudden death (Chugh *et al.* 2008; Shen & Zipes, 2014). The autonomic nervous system (ANS) especially plays an intricate role in the pathophysiology of arrhythmias leading to sudden cardiac death (SCD), and as such, neuraxial modulation is emerging as an important avenue of scientific inquiry and therapeutic intervention (Vaseghi & Shivkumar, 2008; Schwartz, 2014) (Figs 1 and 2).

Anatomy and physiology

To understand the relevance of the cardiac nervous system in the evolution of cardiac disease (Armour, 2008; Kember *et al.* 2013*b*; Florea & Cohn, 2014; Fukuda *et al.* 2015), one must appreciate the anatomical foundations of its functional organization for cardiac control. As a corollary, to develop targeted neuromodulation therapies to treat specific cardiac pathologies, one must comprehend the anatomical basis of neuraxial coordination of regional cardiac function (Buckley *et al.* 2016). Targeted neuromodulatory therapies have been recently devised for sustained treatment of cardiac arrhythmias as well as heart failure. Bioelectric therapies, for example, have proven to be efficacious following myocardial infarction (Beaumont *et al.* 2015), as well as in modulating autonomic imbalances that increase the incidence of ventricular arrhythmias (VAs) (Ardell *et al.* 2015). It is by gaining a thorough understanding of the anatomical basis of neuronal interactivity that one can intelligently devise therapeutic targets for neuromodulation therapy in the management of such disease entities as ventricular arrhythmias (bilateral partial stellectomy) or heart failure (vagus nerve stimulation (VNS) therapy).

Anatomical basis of functional control. A considerable literature exists outlining the gross anatomy of intrathoracic neurons and their ganglia and nerves that innervate the human heart (Kuntz & Morehouse, 1930; Saccomanno, 1943; Mizeres, 1963; Randall *et al.* 1972; Hopkins & Armour, 1984). With respect to the entire cardiac neuraxis, focusing at the level of the heart, human intrinsic cardiac ganglia are known to contain a complex neural network involving different neuronal anatomical subtypes that include unipolar neurons (putative afferent neurons), along with cholinergic and adrenergic neurons that presumably represent the two major motor phenotypes (Hoover *et al.* 2009; Pauza *et al.* 2014). Intrinsic cardiac ganglia also possess relatively large diameter neuronal somata that form clusters of rosettes within single ganglia. These somata frequently project axons centrally to interconnect primarily with dendrites of similar somata within that ganglion, an anatomical arrangement that forms an anatomical substrate for somatal interactions within or among adjacent intrinsic cardiac ganglia, which are second order neuronal interactions. Based on this anatomy, intrinsic cardiac ganglionated plexus neurons may function not only as an efferent neuronal relay station under medullary and

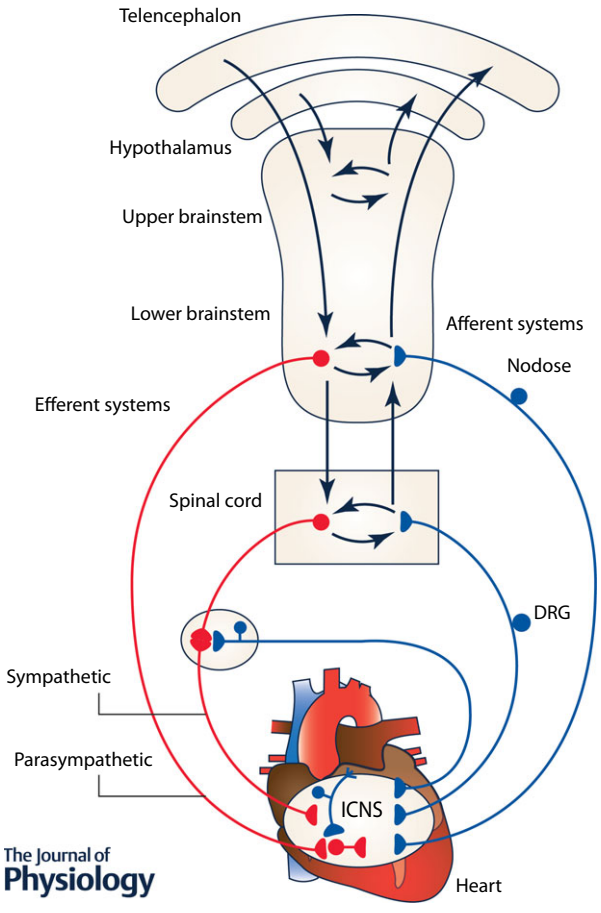

Figure 1. Cardiac neurotransmission
DRG, dorsal root ganglion; ICN, intrinsic nervous system of the heart. Figure modified from W. Jänig (Janig, 2006) with permission.

spinal cord (adrenergic) motor control, but also as an important element in cardiocentric local reflex control (Armour, 2004).

Mammalian intrathoracic extra-cardiac ganglia contain efferent sympathetic postganglionic, afferent and local circuit neuronal somata. In fact, their varied neuronal types and synaptology represents the morphological substrate for various cardiocentric reflexes that depend on peripheral neuronal interactions involved in coordinating regional cardiac indices. These cardiocentric reflexes depend on intrathoracic afferent neuronal transduction of the cardiovascular milieu via intrathoracic local circuit neurons to cardiomotor neurons depicted above.

Cardiovascular afferent neurons. The somata of afferent neurons associated with cardiac or great thoracic vascular mechano- and/or chemo-receptors are located in nodose ganglia (Thoren, 1977; Hopkins & Armour, 1989; Armour *et al.* 1994), as well as through the C6–T6 dorsal root ganglia (Vance & Bowker, 1983; Hopkins & Armour, 1989) bilaterally. The cardiac sensory neurites associated with these afferent somata are located throughout both atria and ventricles, being concentrated in the sino-atrial nodal region as well as in the outflow tracts of each ventricle (Armour & Ardell, 2004). They transduce (1) regional mechanical deformation, (2) the local chemical milieu, or (3) both – thereby displaying multimodal transduction properties, depending in large part in which of the above ganglia they are located (Armour & Ardell, 2004). Most cardiac afferent neurons in intrinsic cardiac ganglia also display multimodal transduction properties. A major exception to such multimodal transduction is the population of sensory neurons in middle cervical and stellate ganglia, associated with mechanosensory neurites

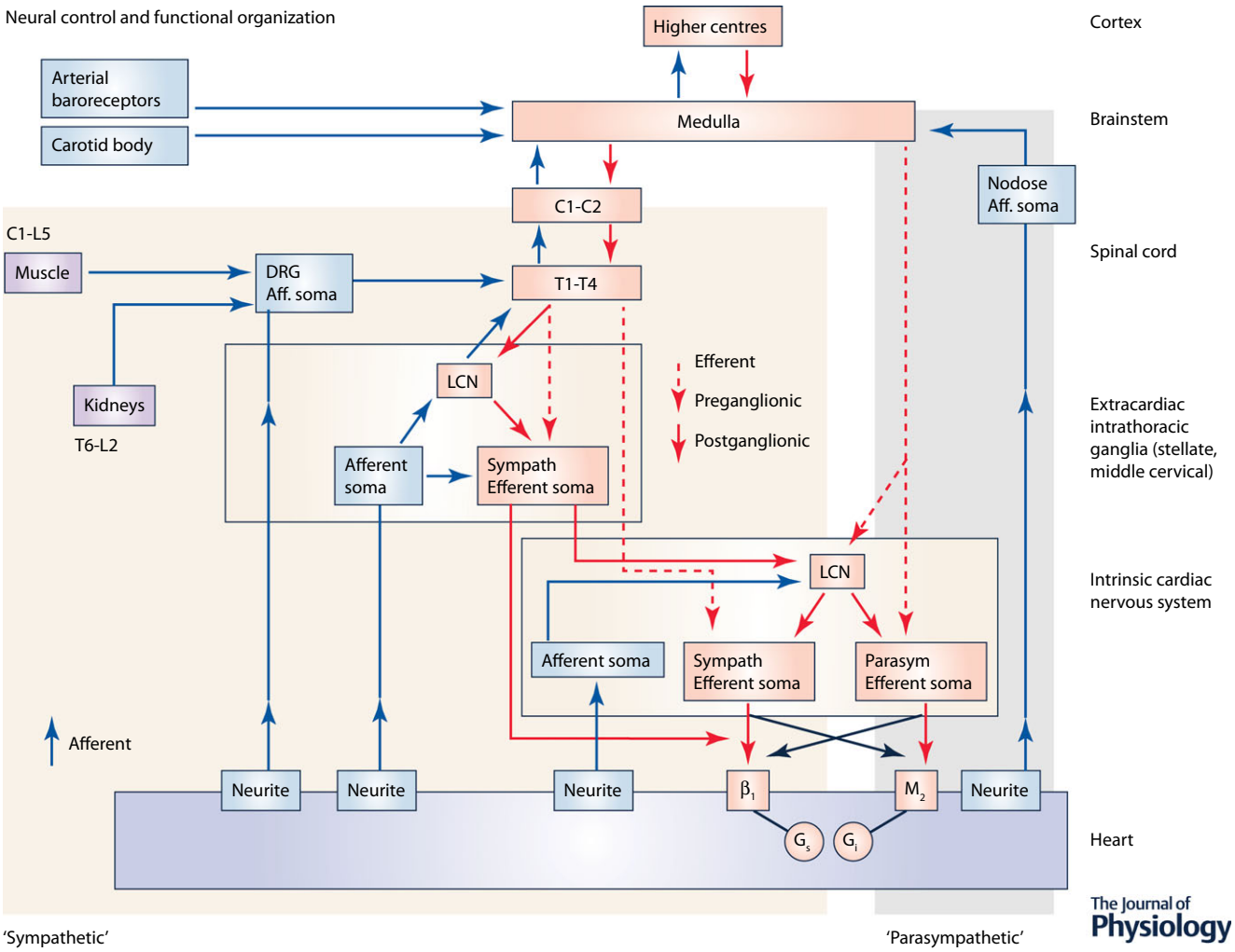

Figure 2. Simplified construct of neurohumoral control and functional organization of cardiac innervation
Aff, afferent; β, β-adrenergic receptor; C, cervical; DRG, dorsal root ganglion; G_i, inhibitory G-protein; G_s, stimulatory G-protein; L, lumbar; LCN, local circuit neuron; M, muscarinic receptor; T, thoracic. Additional pathways, for example nitrergic neurotransmission, are not shown.

located particularly along the inner arch of the aorta (Kember *et al.* 2004),(Armour & Ardell, 2004). Their inputs initiate central (nodose and dorsal root ganglion) and peripheral (intrathoracic extra-cardiac and intrinsic cardiac) reflexes (Armour & Ardell, 2004).

Cardiac motor neurons. Cardiac motor neurons have long been classified as belonging to the cholinergic *versus* adrenergic categories of the ANS. These two motor neuronal populations generally exert opposing effects with respect to the electrical and mechanical indices of the atria and ventricles.

Cholinergic efferent neurons. The somata of medullary parasympathetic efferent preganglionic neurons innervate cardiac parasympathetic efferent postganglionic neurons located in every major intrinsic cardiac ganglionated plexus. Their preganglionic components are located primarily in the ventral lateral region of the nucleus ambiguus, with fewer being located in the medullary dorsal motor nucleus and a scattering of somata located in the intermediate zone between these two medullary nuclei (Hopkins *et al.* 1996).

Parasympathetic efferent postganglionic neurons found in individual atrial or ventricular ganglionated plexi receive input from both vagal trunks. In turn, parasympathetic efferent postganglionic neurons located in individual atrial and ventricular ganglionated plexi influence both atrial and ventricular tissues. Therefore, cholinergic motor control of the heart is widely distributed (Ardell *et al.* 2015).

Adrenergic motor neurons. Cardiac-related sympathetic efferent *pre*-ganglionic neurons located in the intermediolateral cell column of the spinal cord project axons via C7–T6 rami (Norris *et al.* 1974, 1977) to cardiac *post*-ganglionic neuronal somata located in superior cervical, middle cervical, mediastinal ganglia and stellate ganglia (Hopkins & Armour, 1984). Given that direct innervation from T3–T4 ganglia to the heart has not been confirmed, it is possible that fibres from these cardiac neurons travel up to the stellate ganglion, and join cardiopulmonary nerves as they travel to the heart (Janes *et al.* 1986). This is an area that requires more study.These postganglionic neurons from sympathetic ganglia synapse in atrial and ventricular myocardium, releasing noradrenaline at their nerve terminals, in addition to other neurotransmitters, such as neuropeptide Y and galanin, which can inhibit acetylcholine release from parasympathetic terminals (Herring *et al.* 2008, 2012). The middle cervical ganglia, which reside superior to the stellate ganglia, contain many cardiac sympathetic neurons that send direct projections to the heart as well as interneurons that mediate cardiac reflexes (Armour, 1985; Kostreva *et al.* 1985; Tomney *et al.* 1985). In addition, there are multiple afferent mechano-sensory fibres that travel from the heart, and either synapse within the middle cervical or stellate ganglia or transit through these ganglia and synapse in the dorsal root ganglia of the spinal cord, transmitting information from the heart to the central nervous system (Malliani *et al.* 1973; Bosnjak & Kampine, 1989). Efferent postganglionic neurons throughout any peripheral sympathetic ganglia target all cardiac regions. Thus, no anatomical topology exists within peripheral autonomic ganglia with respect to the clustering of sympathetic efferent postganglionic neurons which innervate specific cardiac regions (Armour & Ardell, 2004). Sympathetic efferent postganglionic neurons in any major atrial or ventricular ganglionic plexus exert control over widely divergent regions of the heart (Cardinal *et al.* 2009). It should be recalled that such divergence of control resides within its local circuit neuronal populations.

Anatomical basis of peripheral neuronal interactions – fundamental importance of intrathoracic local circuit neurons. Intrathoracic ganglia have long been considered to act as simple efferent monosynaptic relay stations. In such a thesis, they represent waystations that distribute centrifugal efferent sympathetic *vs.* parasympathetic information from spinal cord and medullary neurons to cardiac tissues, in a reciprocal fashion (Mitchell, 1956; Levy & Zieske, 1969; Henning *et al.* 1990; Carlson *et al.* 1992). The intrinsic cardiac nervous system – as a parasympathetic efferent neuronal way station – acts to suppress cardiac indices all under central neuronal control (Henning *et al.* 1990).

The mammalian intrinsic cardiac nervous system processes both centrifugal and centripetal information in the ongoing coordination of regional cardiac indices (Armour & Ardell, 2004). In that regard, it is relevant to understand that intrathoracic ganglia, including those on the heart, contain a sizable population of neurons which do not project axons out of their respective ganglion or ganglionated plexi to neuronal somata restricted to other intrathoracic ganglia (Murphy *et al.* 1994; Sica *et al.* 1994; Yuan *et al.* 1994; Armour & Ardell, 2004). Neurons projecting axons solely to adjacent neurons are called interneurons. Those which project axons to neurons in other intrathoracic ganglia have also been termed local circuit in nature (Armour & Ardell, 2004). In a number of instances their anatomical arrangement is such that their somata form rosettes in intrathoracic ganglia, projecting centrally in their respective ganglion to solely interact with other somata within one ganglion. In this arrangement – individual neurons only interacting with adjacent somata – presumably is one anatomical substrate for peripheral interactivity (Armour, 2004). Presumably such an anatomical arrangement forms part of the basis whereby significant populations of intrinsic

cardiac neurons, for instance convergent local circuit neurons (Beaumont *et al.* 2013), initiate interneuronal interactions in the periphery (Armour & Ardell, 2004). Such local control persists when the intrinsic cardiac nervous system is chronically disconnected from neurons in the intrathoracic extra-cardiac ganglia and the central nervous system (Ardell *et al.* 1991).

The complexity of peripheral anatomy, upon which functional interactions occur among intrinsic cardiac neurons, has been described. Additional interactions with intrathoracic and central neurons in normal cardiac control add even more complexity (Kember *et al.* 2013*b*). As such, intrathoracic neurons interact not only with neurons in their same ganglion, but also with neuronal somata in other intrinsic cardiac ganglia via axo-axonal and axo-dendritic synapses (Gray *et al.* 2004). They also do so with neuronal somata in intrathoracic extra-cardiac ganglia, providing overall cardiocentric control (Ardell *et al.* 2015; Beaumont *et al.* 2015). The synaptology of such interactivity employs various neurotransmitters, including a variety of peptides, excitatory and inhibitory amino acids, nitric oxide donors, etc., all under the control of central neurons (Yuan *et al.* 1994; Armour, 2004).

Peripheral (intrathoracic) control. While our understanding of the anatomical basis of the multitude of central and peripheral reflexes in which such neurons are engaged remains incomplete, a tentative organization of the intrathoracic cardiac nervous system has been proposed in which cardiac afferent neurons influence, primarily via local circuit neurons, autonomic motor neurons via multiple feedback loops (Armour & Ardell, 2004). For instance, the varied peripheral (intrathoracic) reflexes so engendered represent cardio-centric short-loop reflexes that regulate cardiodynamics on a beat-to-beat basis. They continue to do so even when the intrathoracic nervous system is disconnected from the central nervous system (Arora *et al.* 2000; Murphy *et al.* 2000). In addition, it should be appreciated that a number of neurochemicals modify the neurons involved in intrathoracic extra-cardiac and intrinsic cardiac reflexes (Murphy *et al.* 1994; Yuan *et al.* 1994; Hoover *et al.* 2009). It is known that both excitatory and inhibitory synapses are present in intrathoracic reflexes. How a given population of intrathoracic extra-cardiac or intrinsic cardiac neurons interact in the coordination of regional cardiac indices remains very much dependent on the nature and content of sensory neuronal inputs arising from adjacent cardiovascular structures and from distant tissues (Kember *et al.* 2004). The latter reflect inputs from central neurons that are involved in whole body transduction. Thus, the transduction of the immediate past, as reflective of ganglionic capacity to exhibit memory, is very much dependent upon local circuit neuronal population function (Kember *et al.* 2013*a*).

Perspectives. The anatomical evidence provided above, as related to function, indicates that the peripheral (cervical and intrathoracic) nervous system acts as a distributive processor under the control of the CNS. Its multiple nested feedback control loops, each with different latencies of function, modulates regional cardiac indices throughout each cardiac cycle to assure adequacy of cardiac output in physiological states. What is now becoming evident is the fact that such complex control depends upon the behaviour of its various neuronal elements given the fact that its peripheral reflexes exert considerable influence on regional cardiac rate and force. Thorough understanding of the nerves controlling the heart is a pre-requisite for therapeutic neuromodulation.

Questions and controversies

- What are the functional capabilities of peripheral vs. central reflexes in control of cardiac function?
- What are the roles of support cells (glia) and small intensely fluorescent cells in modulating ganglia function?
- How do sex specific hormonal differences impact autonomic control of the heart?

Cardiorespiratory interactions. There is compelling evidence for strong interactions between cardiac and respiratory control, with such interactions playing an important role in an efficient and effective coordination between the lungs and the circulatory system. This interaction is manifest physiologically by phenomena such as sinus arrhythmia, which consists of cardiac acceleration during inspiration due to the vagolytic effects of lung expansion. Other manifestations are evident using approaches such as frequency domain analyses of breathing, heart rate, blood pressure and muscle sympathetic nerve activity (MSNA) (Pagani *et al.* 1997). Here breathing frequency entrains rhythmic changes in the other three variables. Cardiorespiratory interactions are especially evident in the responses to stressors such as hypoxaemia and hypercapnia. Hypoxaemia affects primarily peripheral chemoreceptors in the carotid bodies and hypercapnia acts mainly through central chemoreceptors in the brainstem. Both hypoxaemia and hypercapnia result in hyperventilation, modest increases in sympathetic nerve traffic to the muscle vascular bed and consequent increases in blood pressure (Somers *et al.* 1989; Somers *et al.* 1992). The overriding importance of hyperventilation in defining the neural circulatory response to hypoxaemia and hypercapnia is evident during apnoea. Lung inflation during hyperventilation acts to inhibit central sympathetic outflow. Therefore during apnoea, absence of lung inflation in the setting of hypoxaemia and/or hypercapnia results in disinhibition of sympathetic

outflow, with consequent marked increases in sympathetic vasoconstrictor activity, and hence in blood pressure (Somers *et al.* 1989, 1995).

In contrast to hypercapnia, hypoxaemia has the added effect of increasing cardiac vagal drive (Daly *et al.* 1979). Again, the cardiovagal response to hypoxaemia is inhibited by lung inflation that occurs as a consequence of hyperventilation during hypoxaemia. Therefore, when apnoea is imposed on a hypoxaemic stress, the absence of lung inflation, with resulting vagal disinhibition, can manifest as significant bradyarrhythmias including prolonged asystole (Fig. 3) (Somers *et al.* 1992). This is part of the diving reflex which allows diving mammals such as sea lions to breathe atmospheric air but still continue to function for extended periods under water. The widespread sympathetic vasoconstriction during submersion and apnoea limits and 'redirects' use of the finite oxygen reservoir preferentially to the heart and brain, which undergo auto-regulatory vasodilatation, at the expense of more 'dispensable' tissues such as the muscle and kidney. Vagally mediated bradycardia enables less myocardial oxygen demand and improved myocardial perfusion due to the prolonged diastole. Evolutionary preservation of the diving reflex in humans, particularly in young children, helps explain the ability of humans to survive prolonged underwater immersion, for periods of up to 30 min (Thalmann *et al.* 2001). With subsequent circulatory, respiratory and renal support, and intensive care, it is possible that these individuals can eventually recover and be physically and neurologically intact despite the extended period of hypoxaemia and apnoea during immersion (Thalmann *et al.* 2001).

While respiratory-mediated chemoreflex activation can significantly influence neural circulatory control, circulatory mechanisms such as the baroreflex can in turn modulate chemoreflex sensitivity. Specifically, baroreflex activation, whether by raising blood pressure using intravenous phenylephrine or by neck suction, can attenuate the ventilatory, sympathetic and vagal responses to activation of the chemoreflex (Heistad *et al.* 1974; Somers *et al.* 1991, 1992). This appears particularly true for the response to hypoxaemia rather than hypercapnia (Somers *et al.* 1991), suggesting a specific interaction between the peripheral chemoreceptors in the carotid bodies and the arterial baroreflex in the carotid sinus, occurring probably at the level of the nucleus tractus solitarii.

Cardiac interoception. Cardiac interoception refers to the process of sensing, storing and representing information about the state of the cardiovascular system (Sherrington, 1961; Cameron, 2002). This information is represented at non-conscious as well as conscious levels (Fig. 4*A*), and a majority of early studies examined non-conscious mechanisms (Ádám, 1998; Dworkin, 2007). Cardiac interoceptive information is relayed predominantly via 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.* 2016), and most cardiovascular diseases

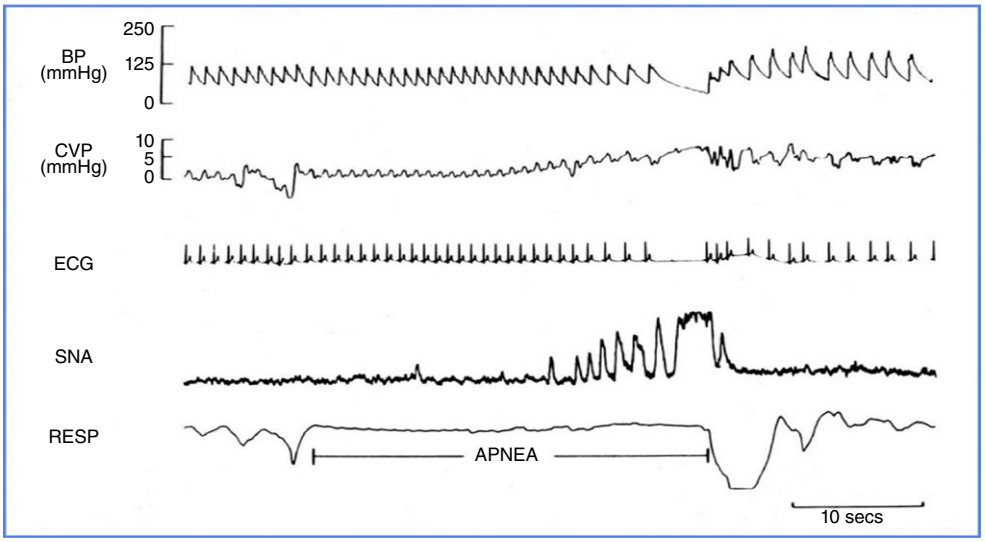

Figure 3. Autonomic influences on cardio-respiratory interactions
Recordings of intra-arterial blood pressure (BP) central venous pressure (CVP), electrocardiogram (ECG), sympathetic nerve activity (SNA) and breathing (RESP) in a healthy young subject during voluntary end expiratory apnoea while awake. Chemoreflex activation during apnoea results in progressively increasing sympathetic outflow to muscle blood vessels, simultaneous with vagally mediated sinus bradycardia with AV block (note the P-wave with absent QRS). The simultaneous activation of vascular sympathetic outflow and cardiac vagal drive during apnoea represents components of the diving reflex. Reproduced with permission from Somers *et al.* (1992).

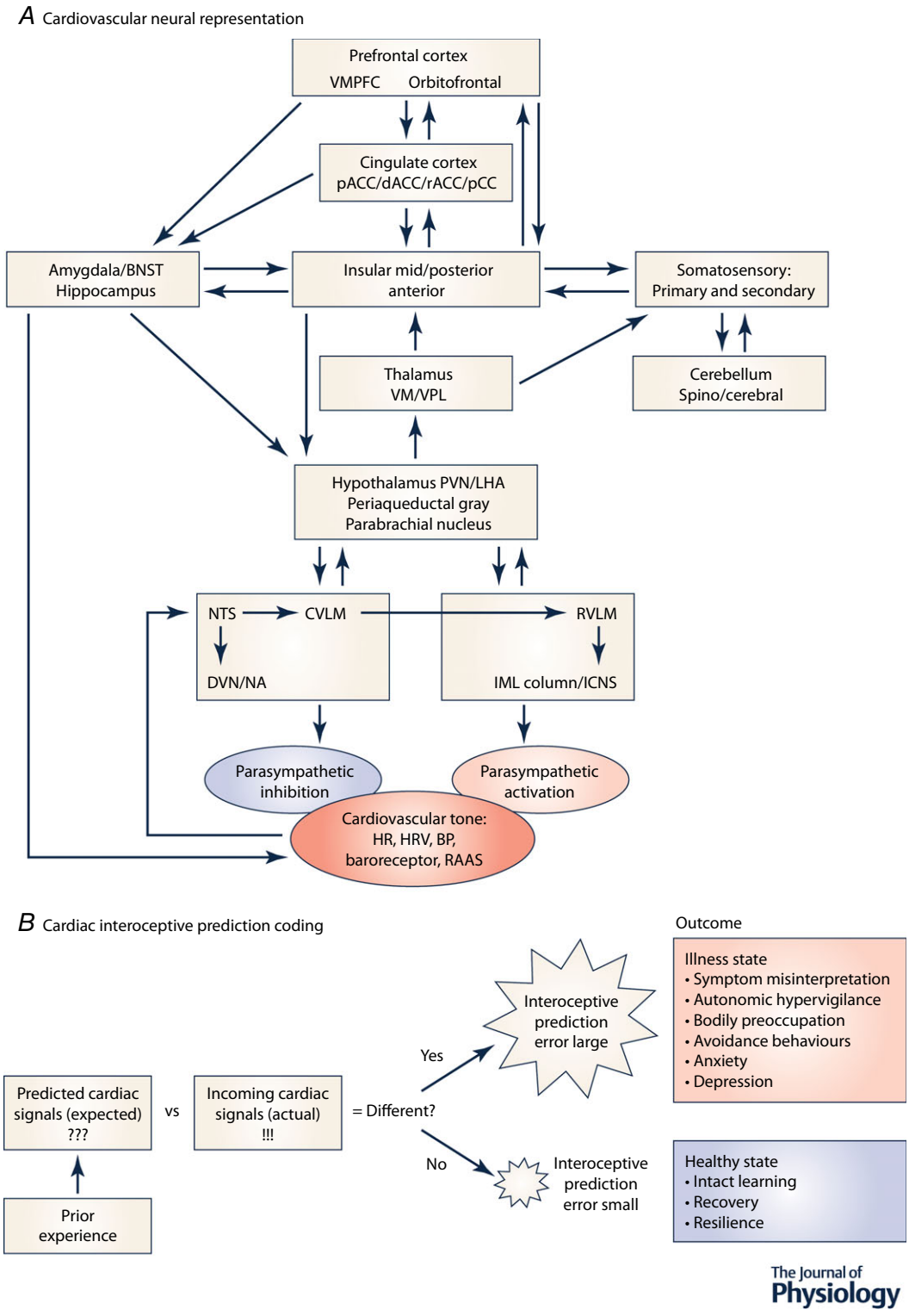

Figure 4. Models of Cardiac Interoception
A, model of cardiovascular neural representation. Cardiovascular information is relayed in ascending fashion via visceral and somatosensory afferent pathways, which project through brainstem and thalamic relay stations, ultimately reaching the insula and somatosensory cortical regions. At each level this sensory information is hierarchically processed, which results in increasingly conceptual representations that are polymodal (i.e. heterogeneous) and can be integrated with emotional states and conscious visceral perceptions. The primary sites

are expressed via abnormalities in these systems. However, cardiac symptoms can reflect very different forms of pathology, or none at all. For example, palpitations can indicate symptoms of a cardiac arrhythmia, a panic attack, or physical exertion. Cardiac patients also occasionally develop comorbid anxiety or depressive disorders, which further complicates the role of interoception and symptom reporting in these individuals.

Measuring cardiac interoception. The methods used to assess human cardiac interoception vary widely. Most tasks assess heartbeat perception under physiological resting conditions. Popular tasks include silently counting heartbeats during pre-specified time periods ('heartbeat counting; Schandry, 1981), tapping a button to indicate each felt heartbeat ('heartbeat tapping'; Ludwick-Rosenthal & Neufeld, 1985), or comparing the heartbeat sensation with tones presented simultaneously or non-simultaneously with the heartbeat ('heartbeat detection'; Whitehead *et al.* 1977; Katkin *et al.* 1982; Brener & Kluvitse, 1988). Each task has drawbacks. Heartbeat counting is confounded by the influence of prior knowledge of one's own heart rate (Ring *et al.* 2015) and reduced sensitivity to heart rate changes (Windmann *et al.* 1999). Heartbeat tapping provides temporal detail about each felt heartbeat (unlike heartbeat counting), but requires a sophisticated analysis approach (Davidson *et al.* 1981; Canales-Johnson *et al.* 2015). Heartbeat detection provides statistical measures of individual accuracy (Schneider *et al.* 1998; Katkin *et al.* 2001; Khalsa *et al.* 2008), but is complex to implement. However, when performed under physiological resting conditions, all of these tasks fail to measure changes in perceived cardiac intensity. This is a key limitation as dynamic disruptions in cardiovascular homeostasis are frequently associated with clinically and/or emotionally significant events. Furthermore, all of these tasks exhibit the finding that cardiac interoception is quite low at baseline. Less than 35% of individuals accurately detect cardiac sensations under resting conditions, suggesting that the majority of individuals do not perceive cardiac sensations at baseline (Jones, 1994). It is possible to more accurately assess individual differences in interoceptive intensity by increasing sympathetic tone. For example, bolus infusions of isoproterenol reliably induce brief increases in cardiac interoception (Khalsa *et al.* 2009*a*). During this 'infusion task', participants concurrently rate the intensity of perceived cardiac sensations while receiving isoproterenol in a double-blinded placebo-controlled manner. At sufficiently high doses cardiac intensity changes are correctly perceived by 100% of individuals. Although this task is invasive, it provides good experimental control over the cardiovascular system and enables accurate measurement of all facets of cardiac interoception, in every subject (Khalsa *et al.* 2015*a*).

Factors modulating cardiac interoception. Cardiac interoception decreases with age (Khalsa *et al.* 2009*a*) and increasing body mass index (Rouse *et al.* 1988; Kleckner *et al.* 2015). It increases acutely during exercise (Jones & Hollandsworth, 1981; Montgomery *et al.* 1984; Schandry *et al.* 1993) and after caffeine ingestion (Zoellner & Craske, 1999). Sex differences have sometimes been reported (Jones & Hollandsworth, 1981; Katkin *et al.* 1981), but there is debate whether these reflect true differences (Rouse *et al.* 1988; Ring & Brener, 1992) and there is currently no clear consensus on this question. Similarly, patients with panic disorder frequently report increased sensitivity to heartbeat sensations, but whether that perception of the heartbeat is accurate is unclear. Numerous studies under resting conditions fail to clearly demonstrate whether panic disorder patients perceive heartbeat sensations differently or have a bias towards reporting such feelings (Ehlers & Breuer, 1996; Van der Does *et al.* 2000; Domschke *et al.* 2010). This contrasts with many studies showing that panic disorder patients perceive cardiovascular sensations more intensely when stimulated pharmacologically via caffeine (Charney *et al.* 1985; Zoellner & Craske, 1999), carbon dioxide (Rassovsky & Kushner, 2003), sodium lactate (Dillon *et al.* 1987), yohimbine (Gurguis *et al.*

where conscious integration typically begins is at the level of cortical regions, including the insula, somatosensory areas, hippocampus and amygdala. These representations are modulated predominantly by the medial, orbital and cingulate regions of the prefrontal cortex, which issues visceromotor commands that propagate back through the system resulting in alterations in cardiovascular tone as well as changes in cardiac prediction signals. *B*, cardiac interoceptive prediction coding. The brain's active 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. Boxes with grey outlines indicate neuroanatomical structures, and black arrows indicate anatomical connections. Boxes with blue outlines indicate conceptual processes, and blue arrows indicate information transfer between anatomo-functional systems and conceptual systems. BNST, bed nucleus of the stria terminalis; BP, blood pressure; dACC, dorsal anterior cingulate cortex; DVN, dorsal motor nucleus of the vagus; HR, heart rate; HRV, heart rate variability; ICNS, intrinsic cardiac nervous system; IML, intermediolateral column; LHA, lateral hypothalamic area; NA, nucleus ambiguous; pACC, pregenual anterior cingulate cortex; PVN, paraventricular nucleus; RAAS, renin–angiotensin–aldosterone system; VM, ventromedial nucleus; VPL, ventroposterior nucleus; pACC, pregenual anterior cingulate cortex; pCC, posterior cingulate cortex; VMPFC, ventromedial prefrontal cortex.

1997), cholecystokinin (Schunck *et al.* 2006) or isoproterenol (Pohl *et al.* 1988). Another consideration is whether there is an inherent threshold for cardiac sensation. This threshold is likely to differ from person to person, but might be modulated by organic or psychiatric diseases, and/or past experiences.

Cardiac interoception in cardiovascular disorders. Cardiac interoception is possible when a failing heart is mechanically assisted with external devices (Couto *et al.* 2013), and even when another person's heart is transplanted inside the chest (Barsky *et al.* 1998). This suggests cardiac interoception can include non-viscerosensory pathways. At rest there appears to be no difference in the ability to detect the heartbeat in the chronic period following myocardial infarction (Jones *et al.* 1985) or hypertension (O'Brien *et al.* 1998; Koroboki *et al.* 2010), or following diagnosis with cardiac or non-cardiac chest pain (Schroeder *et al.* 2015). However, several studies have observed heightened cardiac interoception in palpitation patients with abnormal ECGs (Barsky *et al.* 1993; Ehlers *et al.* 2000). The explanatory mechanism for this finding is unknown, though it is possible that palpitations are atypical autonomic events that more clearly differentiate the heartbeat signal from other bodily sensations (Zamir *et al.* 2012). It is well known that some patients with arrhythmias, such as atrial fibrillation (AF), frequently mistake normal heart rhythms for recurrence of AF, or fail to correctly detect the presence of AF (Flaker *et al.* 2005; Hindricks *et al.* 2005). On the other hand, AF patients with anxiety and depression are more likely to incorrectly overestimate the presence of AF (Garimella *et al.* 2015). Whether such patients reflect a unique subpopulation, and whether interventions targeting anxiety and depression can improve AF symptom burden are currently unknown.

Predictive coding and neurovisceral integration. Human studies of cardiovascular sensation support a role for the insular cortex, but they also identify a broader network of cortical brain regions including the somatosensory, anterior cingulate and dorsomedial prefrontal cortices, as well as thalamus and cerebellum (Cameron & Minoshima, 2002; Critchley *et al.* 2004; Khalsa *et al.* 2009*b*; Kern *et al.* 2013). New perspectives also suggest that interoceptive perceptions are constructed by the brain, indicating that interoceptive experiences may substantially reflect predictions about the state of the body (Seth & Critchley, 2013; Barrett & Simmons, 2015). When the actual state of the body differs from the prediction, this results in a so-called 'prediction error' that is followed by active attempts to modulate the relative value of incoming inputs in order to restore balance (Paulus & Stein, 2010) (Fig. 4*B*). The brain may thus try to 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 contributed to a model of neurovisceral integration, which postulates that a series of structures in the brain are hierarchically organized to mediate emotional experience and vagal control (Thayer & Lane, 2000; Lane *et al.* 2009). Greater complexity and differentiation of experience is mediated by intact medial prefrontal mechanisms and greater vagal regulation, which are electrically stabilizing for the myocardium. By contrast, emotional disorders characterized by anxiety and depression are associated with more persistent and unchanging dysfunctional emotional states and reductions in vagal tone (Thayer & Lane, 2000, 2009). The latter is not altered by serotonin-specific reuptake inhibitors (Kemp *et al.* 2010), which are the most frequently prescribed medications for anxiety and depressive disorders. This highlights the need for alternative treatments that are potentially more cardioprotective.

Questions and controversies

- What governs differences in inherent ability to sense the heart? Some patients fail to detect life-threatening pathological alterations in cardiovascular tone (e.g. arrhythmia or myocardial ischaemia), whereas others misinterpret cardiovascular signals and are convinced of impending doom despite a normal workup.
- Does the onset of a cardiac arrhythmia or anxiety disorder enhance the ability to sense heartbeat signals, or conversely, does it increase the brain's prediction bias towards detecting such signals?
- To what extent is the insular cortex responsible for the ability to feel the heartbeat relative to other somatosensory brain regions?
- Is there actually a difference between the sexes in the ability to feel the heartbeat?

Pathophysiology

Myocardial remodelling. The concept and importance of cardiac remodelling are well established. The recognition that cardiac neural structures remodel in a variety of disorders is a more recent observation. Neural remodelling may be positive if it improves organ function, but it may be negative if it leads to electrical instability and arrhythmogenesis. This section will focus on recent developments in our understanding of neural remodelling in human diseases.

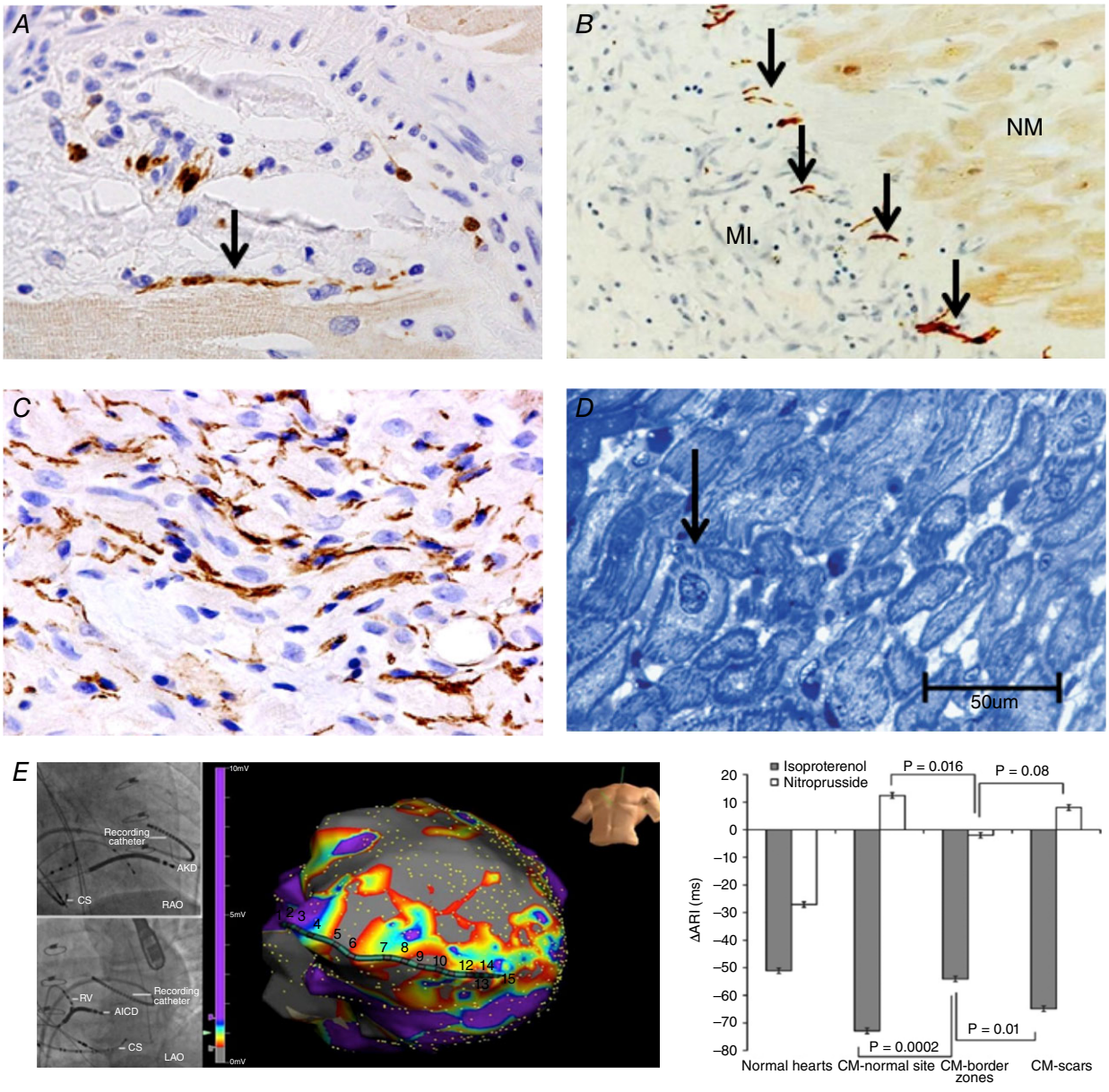

Figure 5. Intramyocardial neural remodelling following cardiac injury
A, nerve sprouting in explanted, transplanted heart, with regions of replacement fibrosis due to transplant vasculopathy (S100 immunohistochemical staining, ×400). *B*, autopsy specimen from a patient dying from coronary artery disease. Note nerve sprouting at junction of healed myocardial infarction (MI) and normal myocardium (NM) (S100 immunohistochemical stain, ×200). *C*, left atrial appendage from patient with coronary artery disease undergoing coronary artery bypass surgery. Note marked nerve sprouting in atrial tissue (S100 immunohistochemical staining, ×400). *D*, pulmonary vein from experimental animal with AF. Note pale cell (arrow) that has morphological features of cells of the conduction system (toluidine blue stain, ×400) (the scale bar for *A*–*D* is shown in *D*). *E*, fluoroscopic location of multi-electrode catheter (left top and bottom) and electroanatomical map (centre) in a patient with ischaemic cardiomyopathy. On the electroanatomical map, the purple areas represent unscarred tissue with normal voltage while the dense grey represents dense scar. All other colours represent border zones (tissue with bipolar voltage $>$ 0.5 mV but $<$ 1.5 mV). Graph on the right shows change in activation recovery interval (ΔARI) from baseline in normal (NL) and cardiomyopathic (CM) hearts in response to isoproterenol and nitroprusside. The ΔARI is greatest in the CM–NL and scar regions of the cardiomyopathic heart. Border zones within each patient are the least responsive to isoproterenol. In response to nitroprusside, the scar and the CM–NL zones are least responsive, or paradoxically increase ARI compared with the border zone regions.

Heart transplantation. There is no argument that the transplanted heart has been separated from all anatomical connections with higher centres of the nervous system. Using quantitative electron microscopic techniques applied to endomyocardial biopsies, Rowan & Billingham (1988) found very few nerves present and concluded that normal myocardial innervation is not likely to be restored in transplanted human hearts. The conventional wisdom that severed nerves have a limited capacity to heal supported the notion that reinnervation of the transplanted heart was unlikely to occur. However, this was challenged by reports of chest pain in patients with transplant-related coronary artery disease. This was strong, perhaps irrefutable, evidence that some patients were experiencing reinnervation of the transplanted heart. Other direct lines of evidence came from the description of vasovagal reflexes in heart transplant recipients (Fitzpatrick *et al.* 1993). It subsequently became established that both sympathetic and parasympathetic reinnervation occurred in some patients (Kim *et al.* 2004), and was associated with improved peak oxygen uptake, heart rate and contractile function during exercise (Schwaiblmair *et al.* 1999; Bengel *et al.* 2001). An autopsy study of 29 patients who died after heart transplantation (Kim *et al.* 2004) found a decrease in total number of nerves (S100-positive) over time, but an increase in growth associated protein 43 (GAP43) positive and tyrosine hydroxylase-positive nerves over time. These findings provided the first histopathological evidence of nerve sprouting (GAP43-positive) and specifically sympathetic nerve sprouting in the transplanted heart (Fig. 5*A*). More importantly, the neural remodelling that occurs in the transplanted human heart has a beneficial effect on cardiac performance (Schwaiblmair *et al.* 1999; Bengel *et al.* 2001). Unfortunately, sudden cardiac death is not uncommon in heart transplant patients (Vaseghi *et al.* 2009). The role of denervation/reinnervation in these deaths remains to be determined.

Ischaemic heart disease. Remodelling of the heart after myocardial infarction (MI) plays an important role in patient outcome. The pioneering work of Drs Jan and Marc Pfeffer established that pharmacological prevention of negative left ventricular remodelling after MI improves survival (Pfeffer & Pfeffer, 1988). In experimental models, much has been learned about remodelling of cardiac and extra-cardiac nerves after coronary occlusion (Vracko *et al.* 1991; Cao *et al.* 2000*a*,*b*; Ajijola *et al.* 2015). Studies of electrophysiological changes within and outside of the infarcted zone have been thoroughly reviewed (Vaseghi & Shivkumar, 2008). There are relatively few morphological studies of neural changes within the human heart after MI. Vracko *et al.* (1991) described the pattern of nerve fibres in human hearts with myocardial scars using S-100 immunohistochemical staining. This method detects Schwann cells but not axons. Nerves devoid of Schwann cells are not decorated, and whether the nerves are sympathetic or parasympathetic cannot be determined. Vracko *et al.* observed increased nerve fibres at the edges of the scar tissue, aligned and oriented in the long axis of myofibres and adjacent to the scars. The investigators postulated that nerve fibres within the infarcted region were destroyed, and that the fibres observed at the edges of the scar tissue were the result of fibre regeneration. Trophic factors, such as nerve growth factor (NGF) and GAP43 have been shown in experimental animals to play a role in the nerve sprouting (Zhou *et al.* 2004). Unfortunately, in experimental systems of ischaemic heart disease, reinnervation is heterogeneous and hyperadrenergic, conditions known to be arrhythmogenic. Infusion of NGF into the stellate ganglion may cause increased cardiac sympathetic nerve sprouting and can facilitate sudden death in dogs with MI (Cao *et al.* 2000*a*) (Fig. 5*B*). Perhaps this is why β-adrenergic blockade reduces the risk of sudden death after MI.

In ischaemic heart disease, neural remodelling is not limited to myocardial structures. Indeed, in experimental systems, neurons and ganglia on the surface of the heart and remote from the heart demonstrate degenerative changes. In an elegant morphological study (Armour *et al.* 1997), epicardial ganglia from patients undergoing coronary artery bypass surgery were removed and studied by electron microscopy. Three types of ultrastructural abnormalities were identified: (1) lamellated inclusions, (2) membrane-bound whorls and parallel arrays of lightly stained membrane with fine granular material, and (3) concentric layers of lightly stained membranes with a darker granular core. These findings help to explain the recognized dysfunction of cardiac ganglionated plexi associated with experimental models of ischaemic heart disease (Huang *et al.* 1993*a*).

While much has been learned about morphological changes in the heart after ischaemic injury, knowledge is incomplete, and the process is complex. There are many factors that promote the degeneration and regeneration of neural structures after injury. It should not be surprising that neural stem cells participate in this process. In rat hearts studied 1 week after coronary occlusion, Drapeau *et al.* (2004) observed nestin-expressing neural stem cells in the myocardial scars. The findings of that study suggest recruitment of stem cells into the infarcted region, contributing to nerve fibre growth in the region of the infarct.

Atrial fibrillation. AF is the most common cardiac arrhythmia, and its complications are associated with significant morbidity and mortality. Morphological changes in the atria include dilatation, fibrosis and degenerative changes in atrial myocytes. A landmark study (Haissaguerre *et al.* 1998) established the importance

of the pulmonary veins in the generation of AF. The pulmonary veins not only contain cardiac-type myocytes, but are also highly innervated (Tan *et al.* 2006). There is growing evidence that remodelling in the left atrium and pulmonary veins contributes to the generation of AF. Much less is known about neural remodelling of the heart and its relationship to AF.

ANS activation has been shown to induce atrial tachyarrhythmias, including AF. The atria are the most richly innervated of the cardiac chambers. There are both intra- and extra-cardiac autonomic nerves and ganglia that have the potential to remodel under a variety of conditions (Tan *et al.* 2006; Arora *et al.* 2007). In fact, labelled sympathetic nerve terminals in dogs with pacing-induced AF showed increased heterogeneous atrial sympathetic innervation (Jayachandran *et al.* 2000). In a similar model, Chang *et al.* (2001) confirmed the increase in sympathetic nerve density. Interestingly, AF and atrial nerve sprouting and sympathetic hyperinnervation also occur in experimental models of MI (Miyauchi *et al.* 2001). Nguyen *et al.* (2009) confirmed these findings in human biopsy specimens of patients who were having coronary artery bypass surgery and suffered from AF (Fig. 5*C*). Currently of great interest is the finding that remodelling of extra-cardiac nerves also occurs in patients with MI, AF and other conditions (Nguyen *et al.* 2011; Ajijola *et al.* 2015). Stimulation or inhibition of selective extra-cardiac neural structures may be a useful therapeutic option of cardiac arrhythmias and other abnormalities.

However, the story is even more complex. Cajal-like cells (Gherghiceanu *et al.* 2008), node-like cells (Masani, 1986), Purkinje-like cells (Chou *et al.* 2005), P cells and transitional cells (Perez-Lugones *et al.* 2003), and melanocyte-like cells (Levin *et al.* 2009) have been identified in human pulmonary veins (Fig. 5*D*). These cells have the potential to contribute to atrial arrhythmogenesis, but a direct contribution of such cells to human AF has not been proven.

Aerobic exercise, an important modulator of cardiac autonomic function, has a variety of beneficial effects on cardiovascular health. However, association between level and intensity of exercise and AF risk is known to exist (Andersen *et al.* 2013). Athletes, particularly as they get older, may be at increased risk for AF (Wilhelm, 2014). Whether this relationship is related directly or indirectly to autonomic function and/or neural remodelling is unknown.

Heart failure. There is ample evidence that neurohormonal activation plays a role in clinical heart failure (CHF). CHF is associated with increased levels of circulating catecholamines and decreased cardiac catecholamine levels. In 1993, in an experimental model of CHF, Himura *et al.* used glyoxylic acid (sucrose–potassium phosphate–glyoxylic acid)-induced histofluorescence and tyrosine hydroxylase immunohistochemical staining to show loss of noradrenergic nerve terminals in the failing ventricles (Himura *et al.* 1993). Cha *et al.* (2008) induced CHF in dogs by rapid ventricular pacing for 5 weeks. All paced dogs had atrial fibrosis, depressed left ventricular function and chamber dilatation. Dogs with CHF had marked heterogeneity of nerve density as measured by GAP43 immuno-staining with an overall decrease in nerve density. Of interest, dogs with the most nerves had a greater incidence of sudden death, while those with the fewest nerves had the lowest cardiac output. The investigators treated some dogs with omapatrilat, a vasopeptidase inhibitor that inhibits the renin–angiotensin system as well. The omapatrilat administration prevented the functional decline and negative myocardial and neural remodelling in CHF animals. While elevated sympathetic activity appears to be detrimental to the heart, parasympathetic stimulation appears to be cardioprotective, providing the basis for investigation of vagal stimulation for the treatment of cardiac disease (Li *et al.* 2004).

Myocardial infarction, in addition to causing formation of scars, leads to partial denervation of the fibres that innervate the myocardium at sites of injury. Given that the majority of the neuronal cell bodies whose axons have been damaged lie within the intrinsic cardiac ganglia and remain intact (Janes *et al.* 1986; Huang *et al.* 1993*b*; Yuan *et al.* 1994; Beaumont *et al.* 2013; Rajendran *et al.* 2016), re-innervation occurs after myocardial infarction, with evidence of nerve sprouts observed at the border zones of infarct (Cao *et al.* 2000*a*,*b*). These regions of denervation with nerve sprouts create heterogeneity in innervation, which is associated SCD risk. However, the functionality of these nerve sprouts remains unknown. In 1983, Barber and colleagues reported that infarcted in addition to viable regions distal to the infarct in a canine model no longer showed evidence of effective refractory period shortening in response to stellate stimulation, implying that many regions of the infarcted heart remained denervated. Furthermore, these regions had an exaggerated response to noradrenaline infusion, called denervation supersensitivity, suggesting that significant heterogeneity in response to circulating catecholamines might also be present in infarcted hearts. Whether these phenomena, however, existed in humans with MI and ischaemic cardiomyopathy (ICM) remained unknown. Vaseghi and colleagues studied the response to sympathetic activation in patients with ICM and ventricular tachycardia and compared them to control patients with normal hearts. They assessed the response of scar, border zone and viable regions in infarcted hearts to normal hearts after infusing isoproterenol, a direct β-1 and β-2 receptor agonist, and nitroprusside, which cause reflex activation of sympathetic nerve fibres in response to hypotension. They measured activation recovery interval (ARI), a surrogate of action

potential duration, and found that in infarcted hearts, ARI did not shorten in response to nitroprusside, even in viable peri-infarct regions, suggesting significant denervation, while all regions in control hearts showed evidence of ARI shortening (Fig. 5*E*). Furthermore, in response to isoproterenol, all regions in infarcted hearts showed a greater response (greater decrease in ARI) as compared to control hearts, confirming that denervation supersensitivity exists in patients with ICM and ventricular arrhythmias (Vaseghi *et al.* 2012).

Extra-cardiac neuronal remodelling. Following ischaemic and non-ischaemic cardiomyopathy (ICM and non-ischaemic cardiomyopathy (NICM), respectively), alterations in the structure, neurochemical phenotype, and function of neurons within the cardiac neural hierarchy but extrinsic to the heart occur (Fukuda *et al.* 2015). These sites include the stellate ganglion (SG), brainstem and higher brain centres.

Intra-thoracic ganglia. Studies of the intrathoracic ganglia, such as the stellate ganglia, have demonstrated enlargement, increased dendritic sprouting and neurochemical changes in SG neurons in animal models of ICM and NICM (Kanazawa *et al.* 2010; Han *et al.* 2011; Ajijola *et al.* 2015). From a mechanistic standpoint, studies in animal models in part link deregulated nitric oxide signalling (Li *et al.* 2007, 2013), and its subsequent impact on calcium handling in SG neurons (Wang *et al.* 2007; Lu *et al.* 2015), with enhanced sympathetic outflow seen in the hypertension, with implications for other causes and types of cardiovascular disease.

In humans, evidence of histological changes in ganglia associated with cardiac disease (sudden death in this case), was first reported by James *et al.* (1979). They reported on two women with sudden cardiac death, and post-mortem findings of inflammation within cardiac ganglia (i.e. epicardial and intra-myocardial ganglia). The term 'ganglionitis' was used to describe this phenomenon, and its associated malignant cardiac rhythm. A decade later, Pfeiffer *et al.* (1989) described the first case of a young patient with a structurally normal heart, but with severe inflammation of the SG, linking viral-mediated neuronal dysfunction in SGs to malignant arrhythmogenesis in this patient. Recently, in patients with congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), Rizzo *et al.* (2014) observed evidence of T cell-mediated inflammation. In ganglia from patients with LQTS and CPVT, when compared to SG from control subjects with accidental death, $CD3^+$ and $CD8^+$ cells were present in greater quantities. Further, there was evidence of inflammation albeit low grade in all LQTS/CPVT patients studied.

Histological evidence of remodelling in stellate ganglia of patients with cardiopulmonary disease was first presented by Docimo *et al.* (2008). They observed an increase in the number of nerve cell bodies within the left SG (LSG) of cadaveric subjects with cardiopulmonary disease, compared to other causes of death. In a follow-up study (Wood *et al.* 2010), the authors correlated fibrosis within the myocardium of cadaveric subjects (a marker of ICM), with the number of nerve cell bodies in the LSG, the implication being that ICM is associated with increased SG neuronal count. While differentiated stellate ganglion neurons are recognized to be post-mitotic, and not expected to divide, the mechanism underlying this increase remains elusive.

Consistent with findings in pre-clinical studies demonstrating neuronal enlargement and dendritic sprouting in SGs of animals with myocardial infarction, stellate ganglion neurons from humans with arrhythmias, and both ICM and NICM exhibit remodelling (Ajijola *et al.* 2012*b*). Mean neuronal size was greater in SGs from ICM and NICM patients compared to controls, with NICM demonstrating the largest neurons in the population. In this study the numbers of neurons did not differ across the groups, in contrast to Wood *et al.* (2010) and Docimo *et al.* (2008). Rather, the difference in neuronal size appeared to be a population shift from smaller to larger neurons. Specific findings in addition to neuronal size include *no* difference in the degree of intra-ganglionic fibrosis, synaptic density, or nerve sprouting amongst the groups.

Higher centres. Significant components of aberrant cardiovascular symptoms can arise from changes in higher central nervous system control over medullary sympathetic and parasympathetic output sites. Among the most common syndromes, neural injury that accompanies obstructive sleep apnoea (OSA) and heart failure (HF) have been well documented, and the resulting functional consequences from such damage are substantial. The impaired outcomes in both conditions typically include enhanced and unvarying sympathetic discharge, often a reduction in parasympathetic output, with resulting influences on cardiovascular characteristics, including hypertension, and phase-shifted or unresponsive blood pressure changes to autonomic, ventilatory, or motor challenges.

The sites of injury in OSA and HF preferentially target autonomic regulatory areas, as revealed by a number of structural magnetic resonance imaging (MRI) techniques, including voxel-based-morphometry (Macey *et al.* 2002; Woo *et al.* 2003), T2-relaxometry (Woo *et al.* 2009), and diffusion tensor imaging procedures (Kumar *et al.* 2011, 2012, 2014; Woo *et al.* 2015). Damage is often lateralized (Woo *et al.* 2003); since autonomic regulatory areas are unequally distributed in the left and right sides of the brain, the asymmetric nature of damage contributes to the inordinate sympathetic effects. Thus, in both OSA and HF patients, forebrain areas, such as the right insular cortex,

which plays a significant role in baroreflex modulation, are especially damaged, as is the right ventral medial prefrontal cortex, an essential component for blood pressure mediation, and the hippocampus, a major player in blood pressure control, along with mood and cognition (Woo *et al.* 2009; Kumar *et al.* 2011, 2012, 2014; Woo *et al.* 2015). Although injury is preferentially lateralized, often the damage is bilateral, with asymmetric severity. Other forebrain areas are similarly targeted, including portions of the cingulate cortex and cingulum bundle, and especially the anterior cingulate (Macey *et al.* 2008; Kumar *et al.* 2012), the entire extent of the hypothalamus, including the anterior hypothalamus and basal forebrain areas (Kumar *et al.* 2011). Midbrain and medullary sites are not spared; the raphe system, especially more-caudal raphe nuclei, and the right ventral lateral medullary nuclei are affected (Kumar *et al.* 2011). The cerebellar cortex and deep autonomic nuclei, the fastigial nuclei, which serve to dampen extremes of hyper- and hypotension (Lutherer *et al.* 1983, 1989), are extensively damaged in both OSA and HF subjects (Macey *et al.* 2002, 2008; Woo *et al.* 2003, 2009, 2015; Kumar *et al.* 2011, 2012, 2014). An overview of near-midline structural injury in HF is shown in Fig. 6*A*. Figure 6*B* shows a subset of axonal injury, derived from diffusion tensor imaging procedures in HF subjects.

Close examination of particular autonomic sites, especially the insular cortices, shows a topographical organization within cortical areas that is altered in OSA. The consequences of such injury are found in phase-delayed and muted heart rate responses to a range of autonomic challenges (cold-pressor, hand grip, Valsalva manoeuvre) (Macey *et al.* 2013, 2014). Both phase shifts and amplitude changes are shown in Fig. 6*C*; heart rate responses between OSA and control subjects are shown in Fig. 6*D*.

The autonomic effects extend beyond responses to transient manipulation. The sustained increase in sympathetic nerve discharge in OSA (Fatouleh *et al.* 2014; Lundblad *et al.* 2014), and the poorly controlled hypertension in both OSA and HF patients are well described. In addition, AF is common in OSA (Holmqvist *et al.* 2015), and poorly regulated glucose control, possibly arising from impaired sympathetic regulation of glucagon, as well as other hormonal regulatory deficits in the syndrome, is exceptionally frequent (Rajan & Greenberg, 2015). The mechanisms underlying the remodelling of brain structures, which affect cardiovascular and other autonomic action, remain unclear. Heart failure patients show a high incidence of sleep disordered breathing, and may be exposed to similar epochs of intermittent hypoxia as OSA patients; intermittent hypoxia is especially injurious to both cerebellar Purkinje cells (Pae *et al.* 2005) and cardiac autonomic ganglia in neonatal animals (Soukhova-O'Hare *et al.* 2006; Ai *et al.* 2009). However, many other processes accompany sleep disordered breathing, including significant perfusion changes, alterations in CO_2, and large, transient changes in blood pressure with interrupted breathing. A critical aspect is maintaining the integrity of the blood–brain barrier function, which prevents entry of neurotoxic substances into the brain; however, that integrity is breached in OSA (Palomares *et al.* 2015) and HF subjects.

The evidence suggests that the injuries introduced by OSA and HF modify cardiovascular action, as

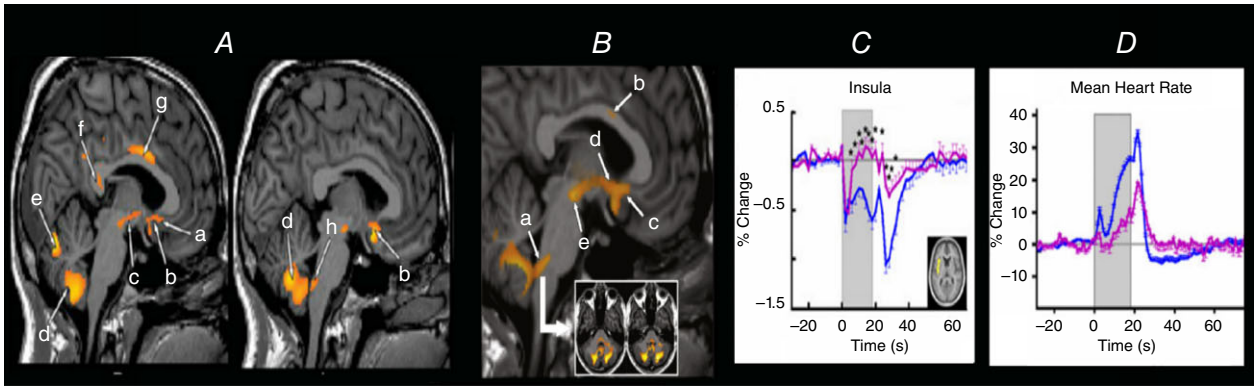

Figure 6. Remodelling in higher brain centres induced by chronic heart failure
A, mean diffusivity, a measure of tissue injury, in a midline and near-midline sagittal view of the brain in 16 HF patients; injury appears in basal forebrain (*a*, *b*), hypothalamic (*c*), cerebellar (*d*, *e*), posterior and mid cingulate (*f*, *g*), and dorsal medullary regions. *B*, axonal injury, indicated by axial diffusivity measures, showing image in axons from the hypothalamus (*c*), through the medial forebrain bundle (*d*), to the pons, and from the midline raphe to the cerebellum (*a*). Injury also appears in the corpus callosum (*b*). *C*, averaged functional MRI signals during the course of three Valsalva manoeuvres from 16 HF patients (red) *vs*. 33 healthy controls (blue); * indicates significance at $P < 0.05$. HF signals are unable to decline to the challenge, and are phase delayed. *D*, heart rate responses in 16 HF subjects (red) *vs*. 33 healthy age- and sex-comparable controls (blue) to three successive Valsalva challenges. The HF subjects show muted and phase-shifted heart rate changes to the challenges.

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 injury.

Questions and controversies

- What are the mechanisms underlying neuronal damage in OSA?
- Can these changes be ameliorated by neuromodulation?
- Is the reversal of pathological neuronal remodelling a return to baseline?
- Why do most OSA subjects remain hypertensive even after breathing treatment?
- Does brain tissue injury recover after heart transplant in HF subjects, or after interventions for breathing in OSA?

Autonomic testing

A number of indices are available to assess autonomic function in humans. Key measurement techniques include heart rate, heart rate variability (HRV), plasma catecholamine spillover and microneurographic recordings of peripheral sympathetic activity. Each of these techniques has strengths and limitations, and the interpretive, logistical and technical challenges of using them vary by several orders of magnitude. Importantly these techniques can be coupled with specific manoeuvres that provide a homeostatic challenge and can be used to diagnose specific autonomic disorders in patients and the response to therapy (Low, 2003). In this context, the utility of several commonly employed tests will be highlighted next.

Sympathoexcitatory stressors. Several forms of acute sympathoexcitatory stress can be used to test autonomic responses in humans. Most commonly these include mental stress of various forms, the cold pressor test and isometric handgrip exercise (Liu *et al.* 2009). After a period of baseline measurements several minutes of stress are imposed and the responses of interest are measured. These responses might be as simple as blood pressure and heart rate or include the more complex measures mentioned above. Importantly, in normotensive subjects the pressor response to acute sympathoexcitatory stress is highly predictive of the future risk of hypertension (Matthews *et al.* 2004). Additionally, isometric handgrip exercise and several minutes of post-exercise ischaemia can be used to physiologically dissect the mechanisms contributing to the rise in blood pressure associated with this intervention. The initial rise in pressure is driven largely by central command signals from the motor cortex followed by a major contribution from chemo-sensitive afferents in the contracting muscles driving a robust increase in MSNA (Mark *et al.* 1985).

Similar approaches have been used to study the rise in pressure and peripheral vasodilatation in the human forearm during mental stress. In humans mental stress does not cause a clear and consistent increase in sympathetic vasodilator outflow to the forearm but does evoke marked NO-dependent forearm vasodilatation (Dietz *et al.* 1994; Carter & Ray, 2009). This outcome contrasts with many animal species where well-described sympathetic dilator nerves exist in skeletal muscle (Joyner & Dietz, 2003). It is also important for any investigator using mental stress interventions to appreciate that there are complex interactions between the type and intensity of the stressor (puzzles, Stroop colour-word test, mental arithmetic, etc.) and the subject's perception of stress (Callister *et al.* 1992; Joyner & Casey, 2015). Some individuals might respond robustly to one form of stress but not another (Roddie, 1977).

Baroreflex testing. The ability of the autonomic and cardiovascular systems to respond to acute perturbations in blood pressure is largely regulated by stretch-sensitive receptors in the carotid sinus and aortic arch, the so-called arterial baroreflexes (Donald & Shepherd, 1980). These receptors respond to differing amounts of stretch caused by changes in arterial blood pressure and when stimulated by higher pressure they generally evoke reflex responses that serve to lower blood pressure including a reduction in heart rate and reduced sympathetic outflow, with directionally opposite responses seen when blood pressure falls. There are also stretch-sensitive receptors in the heart, great veins and lungs that respond to a number of stimuli related to the 'fullness' of the central circulation (Hainsworth, 2014).

By evaluating the physiological responses to beat-to-beat changes in blood pressure it is possible to use analytical techniques from engineering to calculate the threshold, gain, set-point and saturation characteristics of various baroreflex responses. This can be done using observational techniques and looking for 'spontaneous' sequences of rising or falling blood pressure that are associated with directionally opposite changes in heart rate (Diaz & Taylor, 2006). One general problem with this approach is that during most activities of life when

blood pressure is rising or falling, heart rate is also rising or falling in parallel with the changes in pressure. This means that only a limited number of heart rate and blood pressure sequences can be used in this type of analysis. Oscillations in arterial blood pressure occurring typically at 0.1 Hz in humans, known as Mayer waves, have been linked to cardiac autonomic tone (Julien, 2006). These oscillations are slower than respiratory frequency, and exhibit the strongest coherence to MSNA. Mayer waves have also been reported in other species (0.3 Hz in rabbits, 0.4 Hz in rats and 0.1 Hz in cats). Although the origin of Mayer waves remains debated, it is known that surgical denervation of aortic and carotid sinus baroreceptors eliminates these oscillations, suggesting that the baroreflex causes or at least modulates Mayer waves (Julien, 2006). During states of sympathetic activation, Mayer waves are enhanced, and have been investigated as a marker of sympathoexcitation (Cohen & Taylor, 2002). The clinical usefulness of Mayer waves remain to be determined. While the oscillations show correlation to sympathetic nerve activity in normal subjects, conditions such as heart failure, characterized by chronic sympathetic activation exhibit diminished oscillations. Mayer wave oscillations have been identified preceding vasovagal syncope (Lepicovska *et al.* 1992; ten Harkel *et al.* 1993); however, whether they cause or reflect the underlying haemodynamic and autonomic disturbance also remains unclear.

Another approach to baroreflex testing is to use vasoactive drugs to raise and lower blood pressure and then measure the heart rate or MSNA responses to the changes in pressure (Smyth *et al.* 1969; Rudas *et al.* 1999). The advantage of this technique is that a wide range of pressures can be studied and a comprehensive set of indices of baroreflex behaviour can be generated. However, the stimulus is non-specific with contributions from essentially all of the barosensitive areas noted above. Another issue is that while drug infusions evoke reflex changes in both heart rate and sympathetic activity, these responses are not correlated (Dutoit *et al.* 2010). This means that caution must be used in making broad categorical statements about baroreflex function based on a given test or single physiological variable. When MSNA is the outcome variable of interest, it is possible to link the probability of a sympathetic burst with a given level of blood pressure and generate a relationship that provides insight into variables like gain typically obtained via drug infusions (Kienbaum *et al.* 2001; Wehrwein *et al.* 2010). Selective pressure or suction can also be applied to the neck to temporarily stimulate the carotid baroreceptors in relative isolation (Fadel *et al.* 2003).

It is also possible to evoke baroreflex responses by applying subatmospheric (e.g. negative) pressure to the lower body (LBNP) and cause graded venous pooling and simulate blood loss in humans (Cooke *et al.* 2004). For many years it was felt that low levels of LBNP primarily unloaded the cardiopulmonary receptors and could be used to study their responses. The idea was that 10–20 mmHg of LBNP did not cause measurable changes in arterial pressure and thus provided a 'selective' stimulus to the cardiopulmonary receptors. However, imaging studies demonstrated that even low levels of LBNP caused deformation of the aortic arch and raised questions about the selectivity of low levels of LBNP (Taylor *et al.* 1995).

Finally, tilt table testing and the Valsalva manoeuvre are two other techniques frequently used to study the behaviour of the ANS (Denq *et al.* 1998; Low, 2008). These are especially valuable in the testing of patients for diagnostic purposes, but in general are not as selective as the other laboratory-based techniques noted above. Elevated sympathetic tone and diminished parasympathetic tone are proarrhythmic and the evaluation of the ANS provides information beyond the use of the left ventricular ejection fraction (LVEF). These tests include HRV (Feldman *et al.* 2013; Guyenet *et al.* 2013), baroreflex sensitivity (BRS) (Billman *et al.* 1984; La Rovere *et al.* 1988; La Rovere *et al.* 1998; La Rovere *et al.* 1998), heart rate turbulence (HRT) (Schmidt *et al.* 1999; Ghuran *et al.* 2002), heart rate deceleration capacity (Bauer *et al.* 2006) and T wave alternans (TWA) (Ikeda *et al.* 2006).

Although a variety of tests exist to probe ANS function, they require standardization for accuracy and reproducibility in each lab (Malik, 1996). Some tests are time consuming (e.g. baroreflex testing), unpleasant to the patient (e.g. microneurographic recordings and cold pressor test), and are performed with extensive variability at many institutions. Despite these challenges, reliable and reproducible testing of cardiac autonomic function may have a significant impact in early detection and management of cardiovascular diseases.

Risk stratification

Alterations in autonomic function are often detected in patients with cardiac, and even non-cardiac, medical disease. These alterations are often associated with negative prognostic implications. The most commonly used measures to evaluate cardiac autonomic function rely on quantitating autonomic input at the level of the sinus node, i.e. some evaluation of heart rate or heart rate change. The simplest parameter, heart rate, reflects the net parasympathetic and sympathetic inputs, which in rest conditions in normal subjects is heavily weighted to be predominantly parasympathetic. HRV examines beat-to-beat changes in heart rate, and can be quantified using time domain techniques,

frequency domain techniques, or nonlinear analyses. Other evaluations focus on assessing the response of the ANS to small perturbations, such as changes in blood pressure (baroreceptor sensitivity), premature ventricular complexes (heart rate turbulence), and orthostatic hypotension. As demonstrated in the Swedish Malmo Preventative Study, a prospective study of over 33,000 men (Fedorowski *et al.* 2010), orthostatic hypotension was present in 6.2%, and was associated with hypertension and diabetes. The presence of orthostatic hypotension was associated with increased mortality and coronary event risk, independent of traditional risk factors. Finally, parameters of heart rate acceleration or deceleration with exercise or other conditions also provide a measure of autonomic responsiveness. Virtually all of these techniques provide prognostic information (La Rovere *et al.* 1998; Jouven *et al.* 2005; Exner *et al.* 2007; Lahiri *et al.* 2008; Bauer *et al.* 2009). While the roles for sympathetic activation as a trigger for life-threatening ventricular arrhythmias (Albert *et al.* 2000, 2003; Lampert *et al.* 2002), and for parasympathetic activation's protective effect (Vanoli *et al.* 1991; Ng, 2014) are well established, none of the heart rate-based parameters provides strong enough risk prediction to be useful clinically, particularly for sudden arrhythmic cardiac death. Randomized clinical trials of implantable defibrillator therapy in the early post-myocardial infarction period that have incorporated heart rate and HRV among the inclusion criteria have been negative (Hohnloser *et al.* 2004; Steinbeck *et al.* 2009). While it has been suggested that these parameters are not very predictive of sudden arrhythmic death that is reversible by implantable defibrillator therapy, these trials also included a low left ventricular ejection fraction criterion. Just as low left ventricular ejection fraction may be predictive in other settings, so may these parameters. Yet, in a recent meta-analysis, none of the heart rate-based parameters (HRV, baroreceptor sensitivity, heart rate turbulence) were significant predictors of arrhythmic events in patients with NICM (Goldberger *et al.* 2014).

It is therefore important that alterations in autonomic function are likely to track the severity of the underlying cardiac disease and may serve as a strong or stronger predictor of overall mortality rather than arrhythmic mortality. The trigger for ventricular tachyarrhythmias is often associated with sympathetic activation (Lampert *et al.* 2002), but many of the parameters studied focus on rest conditions or only mild perturbations of the ANS, raising the possibility that these evaluations may not be sensitive enough. In addition, how alterations in autonomic function at the level of the sinus node translate to effects on ventricular electrophysiology, the presumed source for its effect on ventricular arrhythmogenesis, has not been clearly demonstrated.

Questions and controversies

- Why are clinical autonomic indices limited in prediction of sudden death?
- Have autonomic variables largely failed in clinical use due to one-time measurement, rather than dynamic measurements over time?
- How do we develop robust 'reflex' measures of autonomic activity that can be applied easily to a large population?
- What barriers limit translation of population studies of autonomic indices to risk prediction in individuals?
- Is post-exercise vagal tone a useful marker of sudden risk in humans?

In summary, there are several important questions to consider when evaluating the prognostic role of ANS control of the heart in patients with cardiac disease. It is possible that different parameters may be better suited to evaluate overall mortality versus arrhythmic mortality. In particular, evaluation of autonomic control in stress *versus* rest conditions could be an important factor delineating risk. Specifically, assessment of reflex measures of autonomic function provide more information than tonic measures, which are affected by many variables (Wellens *et al.* 2014). In addition, further work focusing on the effects of alterations in autonomic function on ventricular electrophysiology may provide better insight into the risk for developing ventricular tachyarrhythmias.

Clinical management: specific interventions for heart failure, arrhythmias and other cardiorespiratory conditions

Cardiac sympathetic denervation.

Channelopathies. Despite its rapidly growing use in the management of life-threatening arrhythmias, cardiac sympathetic denervation (CSD) is not a novel therapy. Following a series of pioneering interventions which started 100 years ago as reported in detail elsewhere (Schwartz, 2014), the resurgence of interest for this approach was associated with initial reports in 1961 by Estes and Izlar (Estes & Izlar, 1961) and in 1968 by Zipes and colleagues (Zipes *et al.* 1968) for recurrent ventricular tachycardia and subsequently for the congenital long QT syndrome (LQTS) (Moss & McDonald, 1971; Schwartz *et al.* 1975). It was later extended to another channelopathy, catecholaminergic polymorphic ventricular tachycardia (CPVT) (Wilde *et al.* 2008; De Ferrari *et al.* 2015).

To better understand the role of CSD, its anatomical and physiological basis is important. CSD involves removal of the lower half of the stellate ganglion as well as

T2–T4 thoracic ganglia, and is typically performed via video-assisted thoracoscopic surgery (VATS; Figure 7*A* and *B*; Ajijola *et al.* 2012*a*; Vaseghi *et al.* 2014). Thus, the upper half of the stellate ganglia, as well as the middle cervical ganglia, remain intact with this procedure. This also means that despite CSD, some post-ganglionic efferent sympathetic innervation to the heart is preserved. However, since the middle cervical ganglia contain afferent fibres that transit through the stellate ganglia before reaching the spinal cord, afferent neurotransmission through the middle cervical ganglia, in addition to the lower half of the stellate ganglia, is interrupted. Therefore, CSD affects both efferent and afferent sympathetic neurotransmission.

A strong rationale exists for this therapy based on a large series of experimental studies (Schwartz, 2014). The major mechanism underlying the antiarrhythmic efficacy of left CSD (LCSD) is the reduction of noradrenaline release at neural terminals in the ventricles, a factor that increases heterogeneity of repolarization and facilitates the occurrence of ventricular fibrillation (Han & Moe, 1964). The largest series reported so far includes 147 patients and was published in 2004 (Schwartz *et al.* 2004). The number of cardiac sympathectomy procedures (mostly LCSD) being performed has increased steadily, and can be safely done in children and adults (Collura *et al.* 2009). The reported series focused on patients at unusually high risk as demonstrated by the fact that

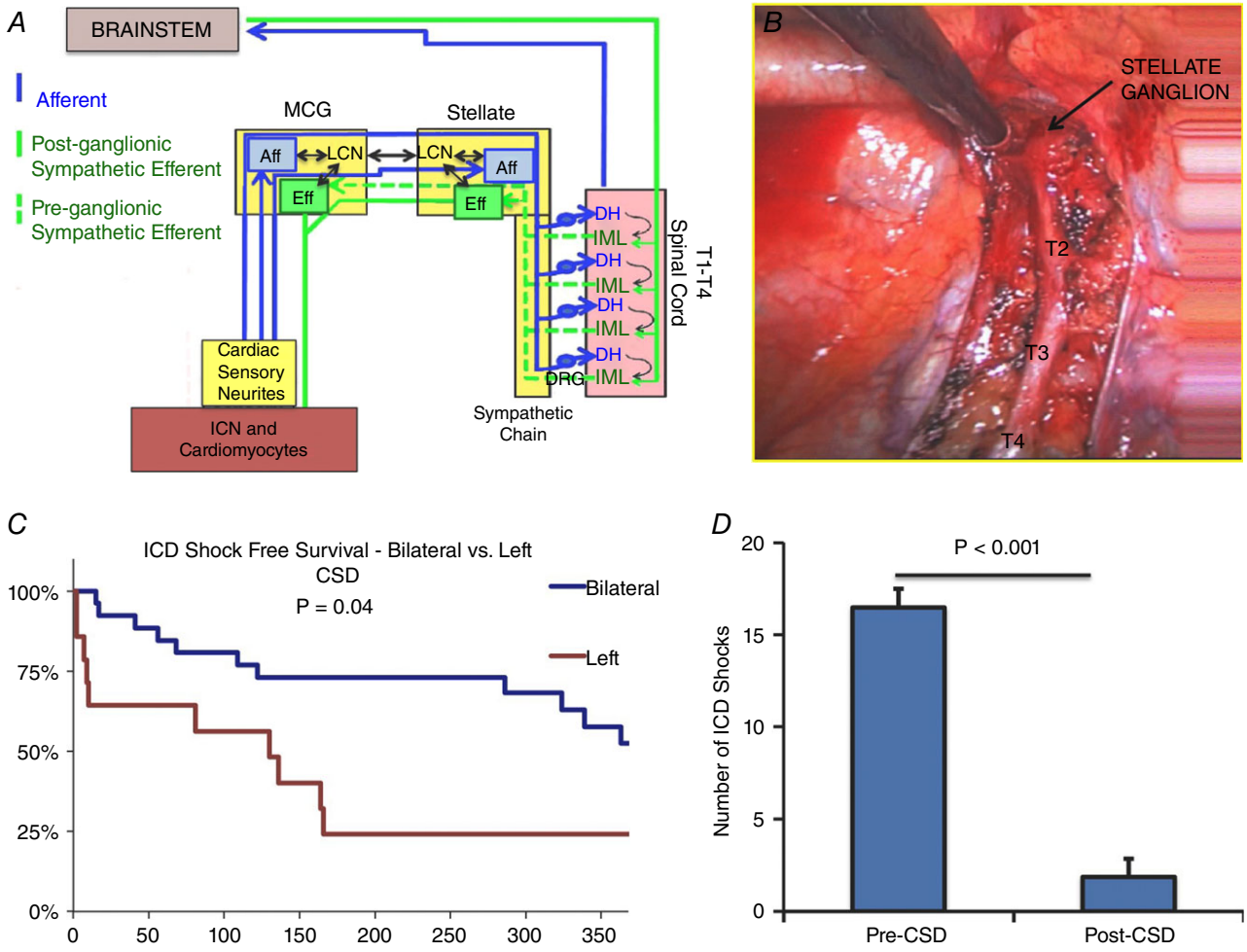

Figure 7. Cardiac sympathetic denervation
Relationship of stellate and middle cervical ganglia are shown. Both ganglia contain interneurons as well as efferent and afferent neurons that both synapse and traverse through the ganglia. Only the stellate ganglia are anatomically connected to the spinal cord. *B*, the left sympathetic chain including the left stellate ganglion as well as the T2–T4 ganglia are shown intra-operatively behind the parietal pleura via video-assisted thoracoscopic surgery. *C*, implantable cardioverter defibrillator (ICD) shock free survival is better after bilateral than left cardiac sympathetic denervation (CSD) in patients with refractory ventricular tachycardia (VT) and structural heart disease. *D*, after CSD, in patient with structural heart disease, the burden of ICD shocks significantly improves at approximately 1 year of follow-up. Aff, afferent; DH, dorsal horn; Eff, efferent; IML, interomediolateral cell column; MCG, middle cervical ganglia.

99% of patients were symptomatic, and among them 48% had survived a cardiac arrest, their QT interval was extremely prolonged (mean QTc 543 ± 63 ms), and 75% continued to have major cardiac events despite full-dose beta-blockade. During an 8 year follow-up, 46% became completely asymptomatic, aborted cardiac arrest occurred in 16% and there was 7% mortality. The mean yearly rate of cardiac events dropped impressively by 91% ($P < 0.001$), and the patients with more than five cardiac events decreased from 55% to 8% ($P < 0.001$). Among patients with electrical storms and multiple implantable cardioverter defibrillator (ICD) discharges, the median number of ICD shocks after LCSD decreased by 95% ($P = 0.002$) from 25 to 0. The conclusion was that LCSD produced a major but incomplete abolition of cardiac events in the high-risk LQTS patients; it was and still is recommended that the primary indication for LCSD is for patients who continue to have syncope despite beta-blocker therapy and for patients with multiple ICD shocks (Schwartz & Ackerman, 2013). In this case LCSD would improve quality of life using the ICD as a safety net. Indeed, the impact of LCSD on quality of life is a very important consideration that often physicians overlook (Antiel *et al.* 2015; Schwartz, 2015). CPVT patients, especially young ones, are not always fully protected by beta-blockers and, as a consequence, usually end up receiving an ICD. Unfortunately for them, the risk of electrical storm is devastatingly high. They are exquisitely sensitive to catecholamines and as the first ICD shock through the pain and fear will lead to catecholamine release, this often initiates a vicious cycle with multiple shocks because of recurrent ventricular tachycardia (VT)/ventricular fibrillation (VF). In 2008 Wilde *et al.* reported for the first time the efficacy of LCSD in CPVT patients (Wilde *et al.* 2008). There were only three patients but the follow-up was very long, exceeding 10 years, and showed a complete suppression of the cardiac events, which in all patients were multiple cardiac arrests. As the most recent guidelines (Priori *et al.* 2013) had considered LCSD only as a Class IIB recommendation, it was felt necessary to provide stronger evidence. Collura *et al.* subsequently reported the benefit of LCSD in two patients with CPVT at mean follow up of 16.6 ± 9.5 months (Collura *et al.* 2009) and a recent worldwide dataset has been reported (De Ferrari *et al.* 2015). This study involved 63 CPVT patients who underwent LCSD and had a mean follow-up of 4 years. There were nine asymptomatic patients, who remained asymptomatic, and 54 patients with major cardiac events. This was a high risk group, as indicated by the fact that 33% had survived ≥ 1 cardiac arrest, that 43% had ≥ 1 appropriate ICD shock, that 26% had ≥ 1 electrical storms. Among these 54 symptomatic patients, 38 continued to have cardiac events despite optimal medical treatment. Within this group the percentage of patients with cardiac events dropped from 100% to 32% ($P < 0.001$) and among the 29 patients with an ICD implanted before LCSD the rate of shocks dropped by 93% (from 3.6 to 0.6 shocks/person/year, $P < 0.001$). In the internal control analysis in which each patient served as his or her own control, there was a 92% reduction in major cardiac events. The important observation was also made that the few instances in which denervation was incomplete (i.e. ablating less than from the lower half of the left stellate ganglion down to the fourth thoracic ganglion) recurrent arrhythmias were noted; this exemplifies the critical notion of the 'adequate dose' of denervation. In 2015, a large Canadian study (Roston *et al.* 2015) on CPVT patients provided additional data on the efficacy of LCSD. In 18 patients who underwent LCSD, the success rate was 89%, almost identical to the worldwide report (Roston *et al.* 2015).

These data force a reassessment of the current clinical approach to the management of CPVT. Beta-blockers should remain the first-line therapy, as they are effective in two-thirds of the patients. The combination of beta-blockers and flecainide appears promising but more long-term data are needed. The present data, showing that 32% of the patients suffer serious ICD-related adverse events within 7 years, should lead to a revision of the guidelines. Indeed, for CPVT patients with syncope despite beta-blockers, it appears that left CSD prior to consideration of an ICD implant is warranted (De Ferrari *et al.* 2015).

Structural heart disease. Multiple accounts of the benefits of CSD have emerged in patients with refractory VT and structural heart disease. (Zipes *et al.* 1968; Nitter-Hauge & Storstein, 1973; Lloyd *et al.* 1974; Schoonmaker *et al.* 1975) However, with the introduction of medications targeting the sympathetic nervous system (including beta-blockers and angiotensin converting enzyme (ACE) inhibitors) that significantly improved the risk of SCD (Kober *et al.* 1995; Hjalmarson, 1997), CSD took a secondary role. It gradually became clear that despite the best available anti-arrhythmic medications and catheter ablation techniques, approximately 30–50% of patients continue to experience recurrent arrhythmias and ICD shocks (Kuck *et al.* 2010; Mathuria *et al.* 2012). In this setting, CSD was once again revived as the therapy to treat recurrent ventricular arrhythmias and ICD shocks.

Given the success of LCSD in hereditary arrhythmias (LQT and CPVT), LCSD was initially tried in a case series of patients with refractory VT/VF storm and structural heart disease (Bourke *et al.* 2010). However, approximately 44% of patients did not benefit from the left sided procedure at follow-up. Of note, in this series, thoracic epidural anaesthesia showed a greater rate of partial or complete response, with approximately 75% of patients having a greater than 80% reduction in their arrhythmias

burden, pointing to the possibility of bilateral CSD, rather than left alone, may provide better results.

To better assess the effects of bilateral CSD, as with any treatment modality with significant translational and retrospective data, randomized clinical trials are critical. To this end, the PRophylactic Cervicothoracic Sympathectomy for PrEVENTion of Ventricular TAchyarrhythmias (PREVENT) has been planned, and is a multi-centre randomized clinical trial designed to assess the effect of CSD in patients with cardiomyopathy who continue to experience ICD shocks despite catheter ablation and medical therapies. The trial, currently registered at clinical trials.gov, is undergoing a feasibility and surgical standardization phase, involving centres both inside and outside the United States, and will provide much needed answers in quantifying the benefit of CSD in the treatment of ventricular tachyarrhythmias.

Questions and controversies

Mechanism of benefit of CSD

- What is the contribution of cardiac de-afferentation to the success of this procedure?
- To what extent are cardiac chronotropy and inotropy preserved after bilateral CSD?
- Is removal of T3 and T4 paravertebral ganglia needed for procedural efficacy?

Role of CSD in other cardiovascular diseases

- Heart failure
- Refractory vasospastic angina

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 (Kamibayashi *et al.* 1995; Oka *et al.* 2001; Mahajan *et al.* 2005; Bourke *et al.* 2010). In patients with refractory ventricular tachycardia (VT) unresponsive to medical therapy and cardiac ablation, Shivkumar and colleagues demonstrated that TEA was highly effective in reducing the VT burden in 75% of the patients (CI 51% to 91%, $P = 0.05$) (Bourke *et al.* 2010). Similarly, Oka and colleagues 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, $P = 0.05$) (Oka *et al.* 2001).

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 (Mahajan *et al.* 2005; Bourke *et al.* 2010). 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 (Olausson *et al.* 1997; Nygard *et al.* 2005). 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.

LSG block is a percutaneous approach to block the peripheral sympathetic ganglia using local anaesthetics. The technique reduces sympathetically driven cardiac excitability in animal and human studies (Nademanee *et al.* 2000; Loyalka *et al.* 2011; Patel *et al.* 2011). Nademanee and colleagues reported that cardiac sympathetic blockade, including LSG block, is superior to the Advanced Cardiovascular Life Support recommended antiarrhythmic therapy in treating patients with electrical storm (Nademanee *et al.* 2000). Long-term survival in patients who were treated with sympathetic blockade was also better, compared to those treated with antiarrhythmics. Reduction in adrenergic tone secondary to blockade of both afferent and efferent sympathetic pathways is most likely responsible for the efficacy of the LSG block. The antiarrhythmic effects of LSG block have also been reported in patients with myocardial infarction (Garcia-Moran *et al.* 2013) Although the therapeutic effects of a single shot LSG block are short lived, Hayase and colleagues have described administering bi-weekly stellate ganglia blocks for 10 consecutive months for effectively suppressing ventricular arrhythmias and ICD shocks in a patient unresponsive to medical therapy and ablation (Hayase *et al.* 2013). In clinical practice, LSG block can induce transient reduction or abolition of VTs during electrical storm and should be considered a temporary measure (analogous to TEA). However it should be noted that the lack of response to LSG block has no impact on predicting the outcome of planned surgical CSD.

LSG block 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 stellate ganglion blocks, unless the patients are being mechanically ventilated.

Questions and controversies

Where in ACLS algorithms should TEA and SG blockade be placed in resuscitation and treatment of electrical storm?

Vagal stimulation – heart failure. Left-sided vagus nerve stimulation (VNS) has been extensively used clinically for the treatment of drug-refractory epilepsy (Ben-Menachem, 2001; Schachter, 2002). It was tested for the first time in patients with heart failure (HF) in a small single-centre feasibility study (Schwartz *et al.* 2008) that was followed by a multicentre international extension increasing the number of patients studied to a total of 32 (De Ferrari *et al.* 2011; De Ferrari & Dusi, 2015). Patients in New York Heart Association (NYHA) class II–III on optimal medical treatment were eligible in the study if they had LVEF $\leq$ 35%; presence of sinus rhythm with 24 h Holter heart rate of 60–110 beats min^{-1} and were capable to perform a 6 min walk test. The primary end-point of the study was the occurrence of all system and procedure-related adverse events (AEs). Secondary end-points were the changes between baseline and the 6-month follow-up visit in the following: NYHA class, quality of life using Minnesota Living with Heart Failure Questionnaire (MLwHFQ), six-minute walk test, LV ejection fraction, LV end-diastolic and end-systolic volumes. Patients were implanted with an electrode on the right cervical vagus connected to a CardioFit stimulator. The CardioFit system (BioControl Medical Ltd, Yehud, Israel) is an implantable vagal neurostimulator system, designed to sense heart rate (via a standard intracardiac electrode) and deliver stimulation at a variable delay (70–325 ms) from the R wave. The stimulation lead is an asymmetric bipolar multi-contact cuff electrode specifically designed for cathodic induction of action potentials, while simultaneously applying asymmetrical anodal blocks that are expected to lead to preferential, but not exclusive, activation of vagal efferent fibres. Electrical stimulation of the right vagal nerve was started 2–4 weeks after implant with a single pulse synchronized per cardiac cycle (duty cycle was 21 $\pm$ 5%). The stimulation current intensity was slowly increased to a maximum of 5.5 mA. The up-titration was generally limited by patient's discomfort or pain, and on average reached an intensity of 4.1 $\pm$ 1.2 mA. Patients were followed at 3 and 6 months thereafter with optional 1 year follow-up.

With the exception of two device-related AEs (post-operative pulmonary oedema, need of surgical revision), the other 24 serious AEs, including three deaths, were adjudicated to be unrelated to the investigational device. Expected non-serious device-related AEs (cough, dysphonia, stimulation-related pain) occurred early but were reduced and disappeared after stimulation intensity adjustment. There were significant improvements in NYHA class, quality of life, 6-min walk test, LV ejection fraction (from 22 $\pm$ 7% to 29 $\pm$ 8) and LV systolic volumes at 6 months. These improvements were maintained (and even magnified) at 1 year (De Ferrari *et al.* 2011). The favourable outcomes regarding feasibility, safety, tolerability and preliminary efficacy 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 *vs.* left vagal nerve stimulation in 60 NYHA II–III patients with LVEF $\leq$ 40% (Premchand *et al.* 2014). The stimulation device and electrode were similar to those used by Cyberonics (Houston TX, USA), and approved for the treatment of epilepsy and previously assessed in preclinical HF studies (Zhang *et al.* 2009); the system does not include an 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. The mean output current at the end of titration was 2.0 $\pm$ 0.6 mA, and this stimulation was maintained throughout the study. 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 the six-minute walk distance. NYHA class improved in 77% of patients. Overall, a modest trend was also observed toward 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 in any of the objective outcome measures (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 had it switched 'OFF' for the first 6 months (De Ferrari *et al.* 2014; Zannad *et al.* 2015*b*). The device, produced by Boston Scientific (Minneapolis, MN, USA) had showed 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 *vs.* 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. Recently, the NECTAR-HF investigators reported the 12 and 18 months follow-up data after therapy was switched 'ON' in the sham-control group at 6 months and remained 'ON' in the active group through out. Although the pre-specified safety endpoint was met and the adverse event and survival rates were within the expected range compared to historical controls, the LV structure and function improved equally in both groups with no difference between the groups (Zannad *et al.* 2015*a*).

How do we explain the differences in the results of VNS seen in CardioFit and ANTHEM-HF compared to those in NECTAR-HF? All the three trials studied very similar NYHA class II–III patients with depressed ejection fraction. Whereas CardioFit and ANTHEM-HF were small open-label studies, NECTAR-HF was a somewhat larger 96-patient randomized, sham-controlled study. The primary safety outcomes were very similar in all the three studies. None of the trials raised any safety concerns. However, whereas CardioFit and ANTHEM-HF showed improvements in cardiac function and HF symptoms, no improvement in LV function was seen in NECTAR-HF. The only major differences in the design of the three trials were in the stimulation parameters used. CardioFit used a stimulation frequency of 1–2 Hz and achieved a stimulation current of approximately 4 mA. ANTHEM-HF used 10 Hz, the natural frequency of the vagus nerve, and achieved a current output of 2 mA, while NECTAR-HF used a much higher frequency of 20 Hz and could only reach 1.2 mA. It is therefore likely that the low current amplitude VNS used in NECTAR-HF and the presence of a control group, albeit with incomplete blinding, may be responsible for the unfavourable study results of NECTAR-HF (De Ferrari, 2014). However, these explanations may be questioned because of the recent announcement of the premature termination of the INOVATE-HF trial for futility. This is a large international multi-centre randomized controlled trial phase III pivotal trial (Hauptman *et al.* 2012), based on the CardioFit pilot study and designed to assess safety and efficacy of vagus nerve stimulation in patients with heart failure with reduced ejection fraction, NYHA class III, LVEF < 40%, left ventricular end-diastolic diameter 50 and 80 mm, in sinus rhythm, receiving optimal medical therapy. The study randomized 725 patients from 80 sites in a 3:2 ratio to receive active treatment or standard optimal medical therapy. The primary endpoint of the study is the composite of all-cause mortality or hospitalization for HF. Although no data are available yet, it is possible that the inclusion of many NYHA class III patients with an implanted cardiac resynchronization therapy (CRT) device (and thus CRT non-responders) may have contributed to the neutral result of the study.

In conclusion, several pre-clinical studies have demonstrated the efficacy of VNS in a variety of heart failure models. Three small clinical studies have demonstrated the feasibility and safety of VNS in heart failure. However, the clinical efficacy results are mixed as noted above. VNS remains a promising therapy for heart failure. However, efficacy may be dependent on appropriate VNS parameters and perhaps patient selection.

Vagal stimulation – atrial fibrillation. Based on the observation that mildly enhanced efferent vagal activity, induced by hypertension, was capable of suppressing PV firing even in the face of little or no heart rate slowing (Tai *et al.* 2000), the Oklahoma group studied the anti-arrhythmic effects of low-level vagus nerve stimulation (LL-VNS) in various canine AF models (Li *et al.* 2009; Sha *et al.* 2011; Sheng *et al.* 2011). LL-VNS was delivered at stimulation voltages below the threshold slowing the sinus rate or AV conduction. Cervical LL-VNS prolonged the atrial and PV effective refractory period, shortened AF duration, and suppressed neural activity of the major atrial ganglionated plexi (GP), as well as right stellate ganglion function (Sha *et al.* 2011). Importantly, stimulating either the right or bilateral vagus nerve produced similar results. The mechanism by which low-level VNS suppresses AF has been implicated by Shen *et al.* demonstrating that the antiarrhythmic effects of LL-VNS may reside in its anti-adrenergic effects, as evidenced by suppression of the neural activity of the left stellate ganglion through upregulation of the small conductance Ca^{2+}-activated potassium channels (Shen *et al.* 2011, 2013). Release of another neurotransmitter (vasostatin-1) by low-level VNS was also implicated as a potential mechanism responsible for its antiarrhythmic effects (Stavrakis *et al.* 2012).

Transcutaneous stimulation of the auricular branch of the vagus nerve (tragus stimulation). A major drawback of cervical VNS is its invasiveness, requiring surgical implantation of a pulse generator and a cuff electrode around the vagus nerve. Common side effects include voice changes, discomfort at implant site and infection (Spuck *et al.* 2010). An alternative to cervical VNS is to stimulate the auricular branch of the vagus nerve (ABVN) located at the external ear. Two locations of the external

ear are richly innervated by the ABVN: concha and tragus (the anterior protuberance of the ear) (Peuker & Filler, 2002). Immersing the central cut end of the ABVN in horseradish peroxidase to trace the projection of ABVN revealed that main nerve terminal labelling was observed in the brain stem nuclei such as nucleus tractus solitarii (NTS) and spinal trigeminal nucleus (Nomura & Mizuno, 1984). It is known that neural output from the NTS projects to the cardiovascular centre, vagal motor nucleus in the brain stem, hypothalamus and cerebral cortex, serving as a 'coordination centre' between afferent neural inputs from peripheral organs and the higher centres of the brain (Boon *et al.* 2001; Ben-Menachem, 2002). The central projection of the ABVN was illustrated by a recent functional MRI study in which widespread excitation of ipsilateral NTS, bilateral spinal trigeminal nucleus, dorsal raphe and locus coeruleus, as well as suppression of the activity of the hippocampus and hypothalamus was elicited by electrical stimulation of the ABVN at 25 Hz (Frangos *et al.* 2015).

Electrical stimulation of the tragus, but not earlobe, helix or antihelix, in human subjects elicited vagus somatosensory evoked potentials evidenced by electro-encephalograpy recordings (Fallgatter *et al.* 2003; Polak *et al.* 2009). Clancy *et al.* applied VNS to the tragus (30 Hz, at sensory threshold) in healthy volunteers and documented that tragus VNS significantly decreased the low-frequency/high-frequency ratio of HRV, as well as the frequency and incidence of the MSNA, indicating a shift of cardiac autonomic balance toward parasympathetic predominance (Clancy *et al.* 2014). Based on the anti-arrhythmic effects of the low-level cervical VNS, the Oklahoma group explored the idea of low-level tragus stimulation (LLTS) at the stimulation level, which did not slow the sinus rate or atrioventricular (AV) conduction. The antiarrhythmic effects were comparable with low-level cervical VNS. In a canine AF model of rapid atrial pacing, LLTS suppressed AF and reversed acute atrial remodelling by lengthening the effective refractory period (ERP) and reducing ERP dispersion, likely by inhibiting the neural activity of the GP (Yu *et al.* 2013). Importantly, antiarrhythmic effects were maintained by stimulation strengths as low as 80% below the threshold that slows the sinus rate or AV conduction. It should be noted that based on recent studies, current delivered at 80% of bradycardia threshold is still 50% above that required to activate descending efferent projections (Ardell *et al.* 2015; Yamakawa *et al.* 2015). These data point to the critical impact of low-level vagus nerve stimulation to impact multiple levels of the cardiac nervous system to impart cardioprotection (Kember, 2014).

Stavrakis *et al.* reported the first-in-man experience of the antiarrhythmic effects of LLTS on patients referred for catheter ablation of drug-refractory paroxysmal AF (Stavrakis *et al.* 2015). The discomfort threshold (tingling sensation at the stimulation site) was measured before anaesthesia and the cardiac threshold (the stimulation voltage slowing the sinus rate or AV conduction) was determined after anaesthesia was started. With only 1 h of LLTS (20 Hz, 50% below the cardiac threshold), the right and left atrial ERP was prolonged, AF duration was abbreviated and systemic pro-inflammatory markers such as tumour necrotic factor-α (TNF-α) and C-reactive protein were suppressed. Notably, the discomfort threshold was significantly higher than the stimulation voltage of LLTS, indicating that LLTS may be used as a non-sentient, outpatient, non-invasive therapy to treat paroxysmal AF.

Spinal cord stimulation. Heart failure is associated with abnormal neuro-hormonal activation leading to therapy with beta-blockers and ACE inhibitors. Spinal cord stimulation (SCS) has been employed for many years to treat patients with intractable neuropathic pain syndromes, pain from extremity ischaemia and non-revascularizable angina. The beneficial mechanisms of SCS may relate in part to modulation of the (alpha) sympathetic tone and/or vagal stimulation. Other mechanisms may be, and probably are, operative.

The purpose of the DEFEAT-HF trial was to test the hypothesis that spinal cord stimulation would improve heart failure metrics including heart size and muscle wall thickness and functional capacity. The trial was a randomized (3:2), parallel, single blind controlled study in patients with (1) NYHA class III HF, (2) LVEF $< 35\%$, (3) QRS duration < 120 ms and LVEDD > 55 mm. The primary objective of the DEFEAT-HF study was to evaluate the reduction in left-ventricular end systolic volume index (LVESVi) after 6 months of SCS therapy in the treatment arm compared to the control arm (Zipes *et al.* 2016).

Forty-two patients were randomized to SCS ON and 24 to SCS OFF. Among randomized patients, the mean age was 61 years; 79% were male; mean LVEF was 27% and mean QRS duration was 105 ms. The change in LVESVi over 6 months was not significantly different between randomization arms (SCS OFF: -2.2 [95% CI: -9.1, 4.6] *versus* SCS ON: 2.1 [95% CI: -2.7, 6.9]; $P = 0.30$). Analyses of secondary endpoints including peak $\dot{V}_{O_2}$, N-terminal of the prohormone brain natriuretic peptide, freedom from first hospitalization with HF or death at 6 months, change in Minnesota Living with HF quality of life, change in New York Heart class, and change in six-minute hall-walk all showed no differences between groups. For this study, SCS was delivered with a duty cycle of 12 h on and 12 h off. While safety concerns were addressed by this study, the SCS protocol likely was not optimized for cardioprotection. The successful application of SCS is critically dependent on: (1) the location of the electrode interface, (2) the stimulation protocol employed, and (3) the substrate that is being targeted (neural and

cardiac). Future studies should consider these benchmarks as well as evolve appropriate biomarkers to assess efficacy.

Questions and controversies

- What are the optimal stimulation parameters for the vagus nerve in humans?
- What are the specific stimulation parameters that preferentially activate efferent vagal fibres over afferent fibres?

Ganglionated plexi and vein of Marshall ablation. The intrinsic (ICN) and extrinsic cardiac innervations play a critical role regulating physiological modulations on the cardiac myocardium. In the atria, such modulation can turn maladaptive and lead to AF. The role of vagal activation in the pathogenesis of certain forms of AF has been long recognized (Garrey, 1924). Experimentally, vagal stimulation – or the administration of acetylcholine – can lead to inducibility of sustained AF (Burn *et al.* 1955; Allessie *et al.* 1977, 1984, 1985), and clinically, some forms of paroxysmal AF may be related to an elevated parasympathetic tone (Coumel *et al.* 1978). Mechanistically, vagal stimulation leads to spatially heterogeneous shortening of atrial refractoriness (Zipes *et al.* 1974; Liu & Nattel, 1997), and cholinergic agonists shorten atrial propagation wavelength (Smeets *et al.* 1986), both promoting the maintenance of AF.

In the anatomical–physiological hierarchy of autonomic control of the heart, the ICN – organized in macroscopically recognizable ganglionated plexi (GP) and ligament of Marshall (LOM) – 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 ICN are the final implementers of the autonomic – and profibrillatory – influences on the atrial myocardium. As such, they are attractive therapeutic targets in patients with AF. In canines, catheter ablation of certain components of the intrinsic cardiac nerves (third fat pad in the right pulmonary artery) leads to elimination of AF inducibility after vagal stimulation (Chiou *et al.* 1997; Schauerte *et al.* 2000).

Translation of these facts to the clinic has not been straightforward. With the advent of pulmonary vein (PV) isolation (PVI) as the established technique for catheter ablation of AF (Haissaguerre *et al.* 1998), its claimed mechanistic underpinning – elimination of PV ectopy as AF triggers – gained widespread acceptance. The ablation sites required for PVI crudely match the location of ICN, and soon after PVI became accepted, its autonomic effects became apparent, either as bradycardic events during ablation (Tsai *et al.* 1999), or as alterations of HRV long term (Hsieh *et al.* 1999). The PVI procedure includes variable extents of ICN ablation, which raises the question of which procedural component is responsible for the therapeutic effect. Indeed, PVI and ICN ablation may be synergistic. Pappone *et al.* reported that when PVI was associated with bradycardic events, subsequent abolition of these reflexes by radiofrequency – an index of ICN denervation – led to superior rhythm control outcomes (Pappone *et al.* 2004). Interestingly, in an acute model of vagal stimulation AF, ablation of ICN was superior to PVI, supporting the hypothesis that the ICN, and not the PVI triggers, were mechanistically more relevant (Lemola *et al.* 2008).

Clinical techniques to target ICN have lacked specificity, in part because most clinical procedures have included variable extents of PVI, and in part because the tools for ICN ablation – most commonly radiofrequency – necessarily destroy adjacent myocardium. Surgical series have reported a successful AF ablation using a combined approach of PVI plus GP and LOM ablation, with successful elimination of AF reported as 65% (Han *et al.* 2009), 81% (Edgerton *et al.* 2010), or up to 86% (Krul *et al.* 2011). In order to discern the relative merits of GP ablation *vs.* PVI, Katritsis *et al.* randomized patients with paroxysmal AF to PVI alone or in combination with additional radiofrequency ablation at sites where parasympathetic reflexes are elicited or at the expected anatomical locations of individual GPs. Success rates at 1 year were 60.6% in the PVI group *vs.* 85.3% in the PVI+GP ablation group (Katritsis *et al.* 2011). Results were confirmed in a larger trial that compared PVI alone, GP ablation alone, and PVI+GP ablation in patients with paroxysmal AF. Success rates were 56%, 48% and 74%, respectively, suggesting a synergistic effect (Katritsis *et al.* 2013). A similar comparison in patients with persistent AF showed that PVI combined with GP ablation was superior to PVI combined with linear lesions (68% success *vs.* 52%, respectively) (Steinberg *et al.* 2013).

Targeting the LOM as part of the GP has been traditionally performed surgically. A percutaneous approach using ethanol infusion in the vein of Marshall (VOM) showed that regional parasympathetic denervation followed (Valderrabano *et al.* 2009). 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). The role of ethanol ablation of the VOM in rhythm control outcomes is being studied in a randomized trial.

Finally, it should be noted that GP destruction is merely a crude approach. The GP contain multiple neuronal populations and various neurotransmitters that could be pharmacologically targeted for anti-fibrillatory purposes.

The use of botulinum toxin to interfere with cholinergic neurotransmission is a first approach in this direction (Oh *et al.* 2011; Pokushalov *et al.* 2015).

Renal denervation. Initial inferences into neuroregulation of renal function were made as far back as 1859, when transection of the greater splanchnic nerve resulted in greater ipsilateral diuresis. The opposite effect was seen with electrical stimulation of the peripheral end of the transected nerve, suggesting that renal sympathetic denervation promoted diuresis, while sympathoexcitation had an antiduretic effect (DiBona & Esler, 2010). This concept was replicated using renal blood flow, where denervation increased blood flow, and stimulation decreased blood flow (Starling, 1908). Utilizing renal sympathetic nerve activity (RSNA) measurements, increasing RSNA via electrical stimulation resulted in increased renin secretion, sodium reabsorption and renal vasoconstriction (DiBona & Kopp, 1997).

Adrenergic innervation of the kidneys, occurring via nerves running along the renal artery to the renal microvasculature and juxtaglomerular apparatus (Barajas, 1964; Barajas & Muller, 1973) therefore represents a target for interruption, to achieve increased blood flow, lower renin secretion rate, vasoconstriction and sodium reabsorption. It is hypothesized that in hypertension, these mechanisms are perturbed. Renal sympathetic outflow is now recognized to be elevated in patients with essential hypertension (DiBona & Esler, 2010; Esler, 2014), particularly the drug-resistant population. It is also known that afferent nerve fibres, utilizing a variety of neurotransmitters, convey mechanical and chemical information to the neuraxis (Liu & Barajas, 1993). Both excitatory and inhibitory reflexes involving RSNA, diuresis, and natriuresis have been described, mediated by afferent nerves (Kopp *et al.* 1985; Stella & Zanchetti, 1991; Ye *et al.* 2002). Removal of both kidneys, the source of afferent signals to the CNS (Converse *et al.* 1992), and dorsal rhizotomy (Campese & Kogosov, 1995) (removal of T9–L1 dorsal roots), resulting in preferential afferent denervation, were shown to decrease hypertension. In humans with end-stage renal failure on haemodialysis and with hypertension, in whom MSNA was elevated, nephrectomy resulted in significant reduction of blood pressure (Converse *et al.* 1992). In a hypertensive model in rats, dorsal rhizotomy abrogated hypertension (Campese & Kogosov, 1995).

These findings and others provided strong rationale for renal denervation (of both afferent and efferent nerves) in humans to reduce hypertension. Percutaneous renal denervation by catheter ablation in the renal arteries has emerged as a promising therapeutic approach in patients with treatment resistant hypertension. 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. Two initial clinical trials (Simplicity HTN-1 and -2) (Krum *et al.* 2009; Esler *et al.* 2010) demonstrated promising results, leading to a larger third trial, Simplicity HTN-3 (Bhatt *et al.* 2014). This third trial, however, failed to show the same promising results as the two prior trials.

As a result, renal denervation is at a watershed, with its future uncertain as a treatment for hypertension. The broad body of published trials does indicate technical efficacy is essential, now that the Symplicity HTN-3 trial (Bhatt *et al.* 2014) is seen to be flawed (Esler, 2014; Kandzari *et al.* 2015). In the words of its co-chief investigator George Bakris, 'it is highly likely that RDN as it was performed in the HTN-3 was technically inconsistent at best, but technically inadequate at worst' (Nathan & Bakris, 2014). The current clinical and research practice of largely restricting renal denervation to the treatment of severe, drug-resistant hypertension flowed from the first Symplicity trial, in which ethical considerations dictated restriction of the procedure to this patient group, to optimize the benefit/risk balance. However, in the new round of trials, inclusion criteria are changing, based more on concepts of hypertension pathogenesis, to include milder, untreated essential hypertension, where a neural pathophysiology is prominent (Esler *et al.* 1990) and to exclude isolated systolic hypertension, where biophysical changes in the aorta are more important than sympathetic nervous system activation.

Procedural issues arising from renal denervation will provide key information for future trials. As an example, a larger number of energy applications per artery, in recent trials, has been reported to produce greater blood pressure lowering (Esler, 2014; Kandzari *et al.* 2015), an effect prominent in the otherwise negative Symplicity HTN-3 trial (Kandzari *et al.* 2015). Why should this be so? In a study in pigs, Tzafriri *et al.* (2015) have demonstrated that previously unexpected denervation technical failures can arise when administered intraluminal radiofrequency (RF) energy does not reach its target – the periarterial sympathetic nerves – owing to energy conductivity and temperature gradients being distorted by regional tissue microanatomical variations. Fibrous muscle sheaths and lymph nodes draw the electric field, increasing the lateral and circumferential extent of the ablation geometry, whereas veins act as an energy sink, limiting ablation depth (Tzafriri *et al.* 2015). The outflow of energy from the electrode toward the targeted nerves is not a predictable, symmetrical cone. Assessment of denervation efficacy with renal noradrenaline spillover measurements in clinical studies reflects this, where it has been documented that achieved denervation differs markedly between individual patients, sometimes being less than 25% (Esler, 2014).

Given this unpredictability, concerning the number of RF energy applications, it appears that 'the more the merrier'.

Of perhaps even greater relevance is improved understanding of the anatomy of the renal nerves, generated from studies on pigs (Mahfoud & Luscher, 2015), dogs (Henegar *et al.* 2015), and humans (Sakakura *et al.* 2014). The renal sympathetic nerves are more distant from the renal artery lumen proximally, and converge on the distal renal artery and the renal artery divisions (Sakakura *et al.* 2014; Henegar *et al.* 2015; Mahfoud & Luscher, 2015), where they are more accessible to administered radiofrequency energy. The essence of this anatomical knowledge has been known for more than 60 years (Oldham, 1950) but typically was not acted on in renal denervation trials, where RF energy was inexplicably preferentially directed into the proximal renal artery (Esler, 2014; Kandzari *et al.* 2015). The evidence from experimental studies on this point is that RF energy delivery into the proximal part of the renal arteries, near the ostia, produces suboptimal denervation, whereas energy delivery into the distal renal arteries and renal artery divisions produces near-complete denervation, uniform between animals (Esler, 2014; Mahfoud & Luscher, 2015). Another important limitation of renal denervation in the long term is the potential for renal reinnervation (Booth *et al.* 2015). This not only has the potential to limit efficacy, but could be pathological if it occurs inappropriately. The 'smart' renal denervation trial of the future will be transformed by new procedural knowledge.

Questions and controversies

- Are there adverse consequences to ganglionated plexi ablation for atrial fibrillation or other conditions including vaso-vagal syncope?
- How does ligament of Marshall ablation impact intrinsic cardiac nervous system function?
- Are the effects of ganglionated plexi and ligament of Marshall ablation durable?
- Is there a future for catheter-based renal denervation through the renal arteries?
- How should future clinical trials be designed to avoid technical failures?
- What are optimal inclusion criteria for patients being enrolled into renal denervation trials? Should documentation of sympathetically driven hypertension be required?
- Do renal denervation trials reflect a regression to the mean?

Sleep apnoea interventions. As discussed earlier, patients with sleep apnoea demonstrate significant autonomic pathology as a consequence of apneic events during sleep (Fig. 8*A*) (Somers *et al.* 1995). Indeed, blood pressure during the night often shows a non-dipper pattern with likely consequences for increased long-term cardiovascular risk. In some patients, acute hypoxaemia may also manifest as bradyarrhythmias and even prolonged systole due to the reflex vagal response to hypoxaemia and apnoea mentioned earlier (Fig. 3) (Daly *et al.* 1979; Thalmann *et al.* 2001). The acute consequences of nocturnal hypoxaemia, apnoea, vasoconstriction and blood pressure surges may also include nocturnal angina (Mooe *et al.* 2000), nocturnal myocardial infarction (Kuniyoshi *et al.* 2008) and nocturnal sudden death (Konecny *et al.* 2010). High sympathetic drive at night appears to carry over into the daytime so that patients with OSA have very high levels of resting sympathetic drive, despite the absence of any other co-morbidity and even though they are breathing normally (Fig. 8*B*) (Somers *et al.* 1995). Heightened tonic sympathetic activation in OSA may contribute to the increased risk for daytime hypertension. It is likely that tonic chemoreflex activation, even in normoxia, contributes to the increased daytime sympathetic activity since exposure to 100% oxygen elicits not only an attenuation of sympathetic outflow but also of heart rate and blood pressure (Narkiewicz *et al.* 1998). This speaks again to the importance of respiratory variables in modulating cardiac function. Indeed patients with borderline hypertension have enhanced chemoreflex responses to hypoxaemia, and tonic chemoreflex drive may be implicated in their high levels of sympathetic activation and elevated blood pressure (Trzebski *et al.* 1982; Somers *et al.* 1988).

Central sleep apnoea (CSA), in contrast to OSA, occurs because of an attenuation of central respiratory drive. These patients often have hypocapnia, and oxygen desaturation during apnoea is less severe than that seen in OSA. CSA is usually seen in patients with heart failure where it can also manifest as the crescendo–decrescendo breathing pattern known as Cheyne–Stokes respiration (CSR). Heart failure patients with CSA–CSR have been shown consistently to have a poorer prognosis, with increased mortality (Somers *et al.* 2008). A recent randomized trial, SERVE HF, investigated whether treatment of central sleep apnoea in stable heart failure patients with systolic dysfunction (LVEF $\leq$ 45%), would be accompanied by reduced cardiovascular morbidity and mortality. Surprisingly this study showed that patients randomized to adaptive servo ventilation (ASV) (positive pressure administration using an algorithm that effectively treats CSA) were in fact associated with increased mortality in the CSA treated group (Cowie *et al.* 2015). Importantly, increased mortality was especially evident in patients with CSR as opposed to CSA suggesting first that these two breathing patterns may be different, and second that CSR may conceivably be protective in patients with systolic heart failure. Preliminary evidence suggests that increased

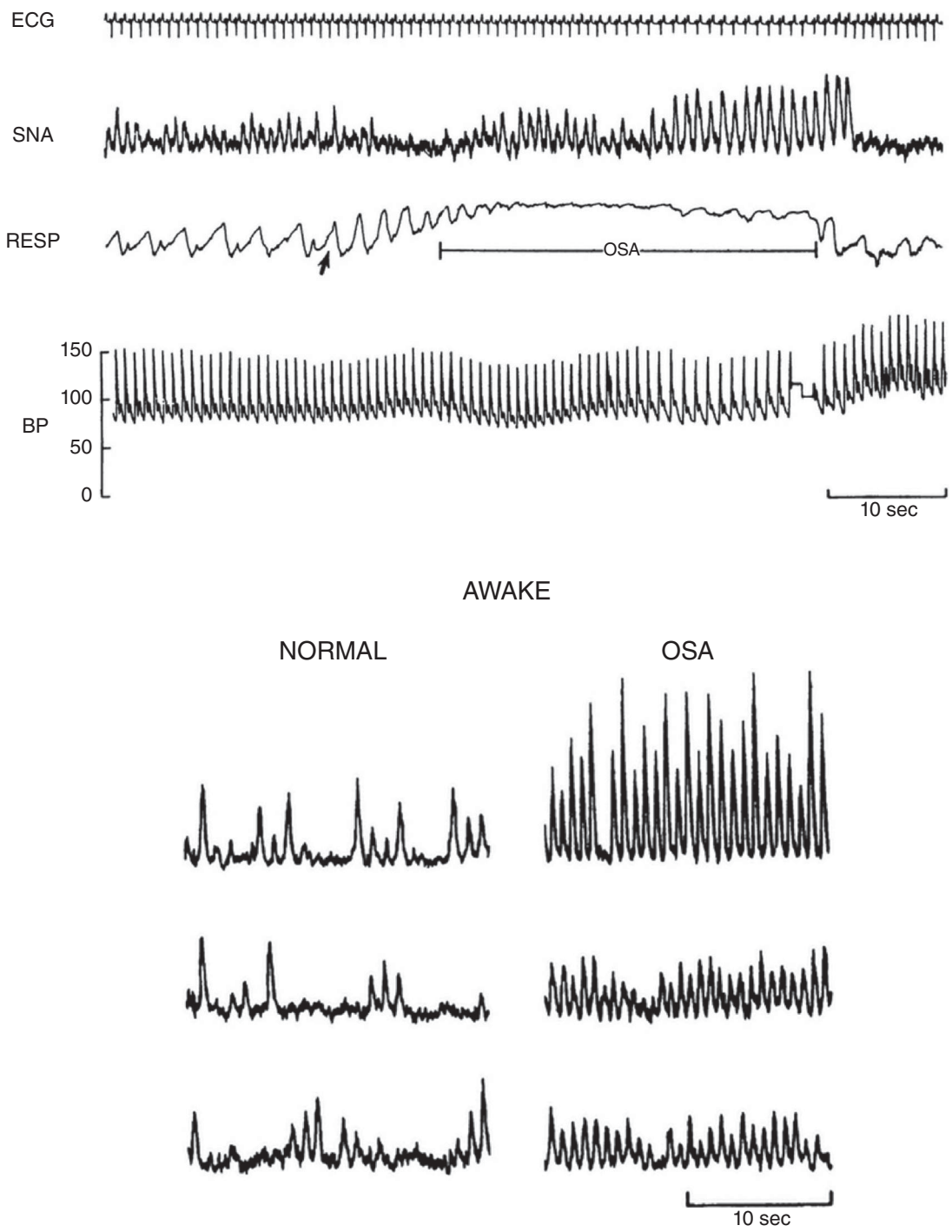

Figure 8. Autonomic dysfunction in obstructive sleep apnoea
A, recordings of the electrocardiogram (ECG), SNA, RESP and BP in a sleep apnoeic patient undergoing continuous positive airway pressure (CPAP) therapy during REM sleep. The arrow indicates a reduction of CPAP from 8 to 6 mmHg, allowing the development of obstructive apnoea, with consequent increased SNA and BP. Reproduced with permission from Somers *et al.* (1995). *B*, recordings of sympathetic nerve activity (SNA) during wakefulness in patients with obstructive sleep apnoea (OSA) and matched controls showing high levels of SNA in patients with sleep apnoea. Reproduced with permission from Somers *et al.* (1995).

cardiovascular deaths in the ASV treated group may have been because of an increased likelihood of sudden death, speaking to the possibility of a protective effect of CSR (Naughton, 2012), perhaps due to an anti-arrhythmic effect of the crescendo–decrescendo breathing pattern.

Questions and controversies

Central sleep apnoea (CSA)–Cheyne–Stokes respiration (CSR) in systolic heart failure

- Whether CSA is a cause or marker of adverse outcomes is not clear. While CSR is often seen in patients with systolic heart failure, and is indicative of a poorer prognosis, is the rhythmic breathing pattern of CSR in fact protective in heart failure, perhaps due to an anti-arrhythmic effect?

OSA and adverse cardiovascular events

- While OSA is associated with increased sympathetic activity, hypertension, atrial fibrillation and increased risk of myocardial infarction and sudden death, particularly at night, does treatment of OSA reduce risk of cardiac and vascular events?

Meditation, holistic interventions and aerobic exercise. Holistic interventions are treatments that address the psychological, social and spiritual needs of an individual in addition to their physical needs. Holistic interventions integrate the context in which an individual's illness arises by carefully attending to the roles played by their values, beliefs, culture and community. They are routinely sought and received outside of traditional healthcare settings, in the form of complementary health approaches. In fact, out-of-pocket expenditure on complementary health approaches outweighs the amount spent on inpatient hospitalizations in the United States (Eisenberg *et al.* 1993; Barnes *et al.* 2004), and more than 30% of adults and 12% of children currently utilize them (Black *et al.* 2015; Clarke *et al.* 2015), often in parallel with allopathic healthcare. Holistic interventions are also being increasingly included within allopathic healthcare services, particularly those delivered by comprehensive care centres such as for cancer (Bultz *et al.* 2014) or terminal illness (Bercovitz *et al.* 2011). The 10 most commonly utilized complementary health approaches are natural products (dietary supplements other than vitamins and minerals) (17.7%), deep breathing (10.9%), yoga, tai chi or qigong (10.1%), chiropractic or osteopathic manipulation (8.4%), meditation (8.0%), massage (6.9%), special diets (3.0%), homeopathy (2.2%), progressive relaxation (2.1%) and guided imagery (1.7%) (Clarke *et al.* 2015). Other utilized approaches include acupuncture, and movement therapies such as pilates and rolfing. Based on these use patterns, it is possible to parse complementary health approaches into two general groups: mind and body practices and natural products practices.

Stress, whether physical or mental, has a major impact on the development of cardiovascular pathology (Nemeroff & Goldschmidt-Clermont, 2012; Thurston *et al.* 2013; Golbidi *et al.* 2015). Early clinical indicators of the link between stress and cardiac arrhythmias identified increased ventricular irritability, arrhythmogenicity and sudden cardiac death during acute mental stressors (Lown *et al.* 1976; DeSilva & Lown, 1978; Lown & DeSilva, 1978; see also Ziegelstein, 2007). Further, strong emotions, including anger are recognized to powerfully modulate ventricular electrophysiology, and risk of arrhythmogenesis (Gray *et al.* 2007; Taggart *et al.* 2011). It is not a rarity for sudden death to be precipitated by a strong emotional outburst. Depression is also associated with increased mortality following myocardial infarction (Frasure-Smith *et al.* 1993, 1995). This relationship appears to be specific to negative affect as opposed to anger or low social support (Frasure-Smith & Lesperance, 2003). Population scale studies have also confirmed causal relationships between strong emotional experiences and acute cardiac events. For example, examinations of emergency department records have identified increased rates of acute coronary syndrome during natural disasters such as earthquakes (Leor *et al.* 1996), but also during major sporting events such as World Cup soccer, when arousal elevations are presumably positively as well as negatively valenced (Wilbert-Lampen *et al.* 2008, 2010; Borges *et al.* 2013). While such occurrences have been sometimes characterized as 'precipitating events' resulting in earlier unmasking of chronic pathology (Schwenk, 2008), emotional stress can also trigger ventricular dysfunction in healthy individuals, through a mechanism ascribed to exaggerated sympathetic stimulation (so called 'takotsubo cardiomyopathy') (Wittstein *et al.* 2005; Templin *et al.* 2015).

It is important to note that several considerations have been raised about this nascent field. These include the observations that many studies have utilized smaller sample sizes or non-randomized interventions, or failed to include adequate comparator conditions to control for non-specific effects associated with intervention delivery (so called 'attentional controls') (Ospina *et al.* 2007; Goyal *et al.* 2014). While the risk of bias is an ever-present concern in any field, and the utilization of appropriate comparators is essential, the non-pharmacological nature of mind–body interventions necessitates the judicious application of principles and methods from the field of behavioural randomized controlled trials. In pragmatic terms, this can sometimes mean that selection of an attention control in clinical settings may not appropriately determine whether a novel intervention shows clinical efficacy at treating illness. In such cases a more suitable

comparator condition might be one in which an intervention's efficacy is compared with usual care, or an enhanced usual care strategy (Freedland *et al.* 2011; Freedland, 2013). On the other hand, an attention control may be more appropriate in cases where the specificity of an efficacious clinical intervention is being investigated.

Investigations of mind and body practices on autonomic and myocardial function are still in the early stages of development. Certain practices seem to induce quiescent autonomic states (Telles *et al.* 1995; Chaya *et al.* 2006) while others induce dynamic changes (Peng *et al.* 2004; Cysarz & Bussing, 2005), presumably through modulations in vagal tone via respiratory sinus arrhythmia. Compassion training may reduce sympathetic nervous system reactivity and improve parasympathetic reactivity during acute mental stress in women (Arch *et al.* 2014). Mindfulness training may enhance resiliency in marines preparing for deployment, by speeding the return to autonomic baseline and dampening viscerosensory reactivity in the central nervous system (Johnson *et al.* 2014). Extending this notion further, an intriguing case report described suggested a novel effect of meditation on the ability to down-regulate elevated adrenergic arousal due to isoproterenol (Dimsdale & Mills, 2002). However, a follow up study failed to replicate this finding at the group or individual level (Khalsa *et al.* 2015*b*).

Recent evidence suggests that mind and body interventions can be beneficial in the treatment of cardiac arrhythmias. A 3-month face-to-face training in yoga and meditation in patients with paroxysmal AF was associated with reductions in episodes of symptomatic AF, symptomatic non-AF episodes, and asymptomatic AF episodes, as well as reductions in heart rate and blood pressure, and improved quality of life indicators (Lakkireddy *et al.* 2013). In a separate study by the same group, neurocardiogenic syncope patients reported reduced syncopal and presyncopal episodes after receiving electronic training in yoga via instructional videos (Gunda *et al.* 2015). A small pilot study showed that mindfulness-based stress reduction effectively reduced anxiety in adolescents with ICDs or pacemakers (Freedenberg *et al.* 2015). While some of these studies lacked comparator groups, and do not identify specific mechanisms underlying the observed effects, they demonstrate the promise and potential efficacy of mind and body interventions on cardiac and psychological outcomes in arrhythmia patients.

Aerobic exercise has long been recognized to improve autonomic balance, by both central and peripheral mechanisms (Billman *et al.* 2015; Haack & Zucker, 2015). In humans with heart failure, ischaemic cardiomyopathy, diabetes and other diseases where autonomic imbalance is known to occur, aerobic exercise is known to improve cardiac autonomic indices (Gordon *et al.* 1997; Laterza *et al.* 2007; Spierer *et al.* 2007; Kleiber *et al.* 2008; Mousa *et al.* 2008; El Mhandi *et al.* 2011; Rodrigues *et al.* 2012, 2014; Zheng *et al.* 2012; Kaikkonen *et al.* 2014; Groehs *et al.* 2015; Masson *et al.* 2015; Sa *et al.* 2016). As exercise has been covered in an accompanying White Paper, we will not focus on it further.

Questions and controversies

Mind and body practices such as yoga and meditation have well-established roles in attenuating autonomic stress, but their role in improving cardiovascular health is less established.

- Do mind and body interventions or their active components modulate information flow (i.e. dysfunctional crosstalk) between interacting feedback loops from the cardiovascular periphery and autonomic and central nervous systems?
- Which mind and body interventions have the greatest reliability and efficacy at improving psychosocial functional impairments in cardiovascular disorders? What is the role of context, e.g. individual vs. group delivery? In person vs. electronic delivery? Traditional (unaltered) delivery vs. active components?

Conclusions

Clinical neurocardiology links the substrate of the heart and the neurohumoral control systems that regulate it, and provides clinically applicable avenues for neuroscience-based therapies. These include (1) identifying patients at high risk for future adverse outcome, (2) helping monitor disease progression and monitoring effect of therapies, and (3) providing novel targets for therapeutics. Neuromodulation strategies show real promise of sustaining cardiac function while maintaining electrical stability. This field requires special efforts in increasing scientific investments on a large scale. In this vein, initiatives such as the 'Stimulating Peripheral Activity for Relieving Conditions' (SPARC) under the guidance of the National Institutes of Health (NIH), will pave the way for improving the efficacy and adverse effects of clinical neuro-modulation.

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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