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TOPICAL REVIEW

What gets on the nerves of cardiac patients? Pathophysiological changes in cardiac innervation

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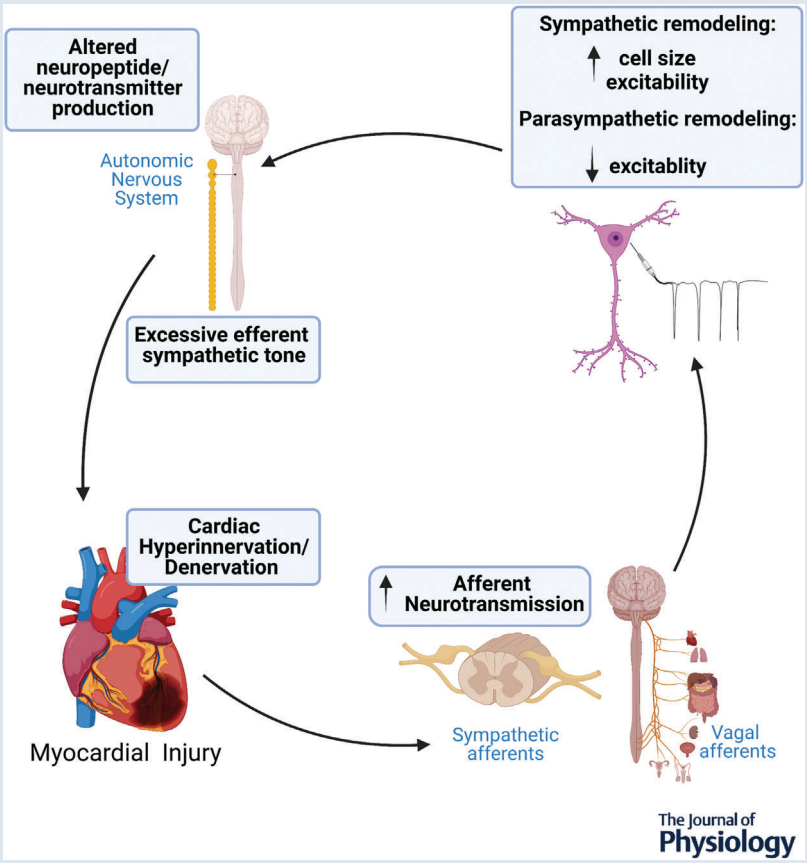

Abstract The autonomic nervous system regulates cardiac function by balancing the actions of sympathetic and parasympathetic inputs to the heart. Intrinsic cardiac neurocircuits integrate these autonomic signals to fine-tune cardiac control, and sensory feedback loops regulate autonomic transmission in the face of external stimuli. These interconnected neural systems allow the heart to adapt to constantly changing circumstances that range from simple fluctuations in body position to running a marathon. The cardiac reflexes that serve to maintain homeostasis in health are disrupted in many disease states. This is often characterized by increased sympathetic and decreased parasympathetic transmission. Studies of cardiovascular disease reveal remodelling of cardiac neurocircuits at several functional and anatomical levels. Central circuits change so that sympathetic pathways become hyperactive, while parasympathetic circuits exhibit decreased

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activity. Peripheral sensory nerves also become hyperactive in disease, which increases patients' risk for poor cardiac outcomes. Injury and disease also alter the types of neurotransmitters and neuropeptides released by autonomic nerves in the heart, and can lead to regional hyperinnervation (increased nerve density) or denervation (decreased nerve density) of cardiac tissue. The mechanisms responsible for neural remodelling are not fully understood, but neurotrophins and inflammatory cytokines are likely involved. Areas of active investigation include the role of immune cells and inflammation in neural remodelling, as well as the role of glia in modulating peripheral neuronal activity. Our growing understanding of autonomic dysfunction in disease has facilitated development of new therapeutic strategies to improve health outcomes.

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Abstract figure legend A summary diagram illustrating the progression of autonomic dysfunction following cardiac injury or disease. Afferent neurotransmission is increased and may contribute to the pathological remodelling of efferent autonomic activity, which is generally characterized by sympathetic hyperactivity and withdrawal of parasympathetic tone. Cardiac injury and disease is also associated with systemic and tissue-specific inflammation, altered neuropeptide and neurotransmitter production, and alterations in cardiac nerve density. Together, these changes in autonomic transmission exacerbate cardiac dysfunction in disease.

Introduction

The autonomic nervous system regulates cardiac function by balancing the actions of sympathetic and parasympathetic inputs to the heart. Multiple feedback loops regulate autonomic balance in the face of external stimuli and allow the heart to adapt to changing circumstances. The heart is densely innervated with sensory, sympathetic and parasympathetic neurons targeting both the myocardium and cardiac conduction systems. These neuronal populations have distinct distributions and phenotypes, and are subject to significant changes in pathophysiological states (Herring *et al.* 2019; Bardsley & Paterson, 2020; Hadaya & Ardell, 2020). This review will summarize the changes that occur in the cardiac innervation during pathology, identify key questions for future research, and highlight promising areas for therapeutic development.

Neural control of the heart in normal physiology

Autonomic control of the heart balances parasympathetic output through the vagus nerve and sympathetic output via paravertebral ganglia (Fig. 1, adapted from Scalco *et al.* 2021). Sympathetic and parasympathetic transmission must be rapidly adapting and highly sensitive to changes in external stimuli, and must exhibit high fidelity of information transfer so that cardiac activity may respond rapidly and appropriately to a constantly changing environment. Disruption of autonomic balance through the loss of parasympathetic drive or enhanced sympathetic transmission to the heart is observed in many pathophysiological conditions.

Decades of study have identified the central neurocircuitry that controls the cardiovascular system, which is briefly summarized here (reviewed by Dampney, 2016; Coote & Spyer, 2018; Scalco *et al.* 2021). Parasympathetic

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control of the heart originates in the nucleus ambiguous and the dorsal motor nucleus of the vagus within the brainstem. Sympathetic control of the heart originates in the rostral ventromedial medulla, rostral ventrolateral medulla, A5 area of the pons, and the paraventricular nucleus of the hypothalamus. The activity of sympathetic and parasympathetic neurons in the central nervous system is influenced by descending signals from higher order cortical nuclei and ascending sensory information that is relayed through the nucleus tractus solitarius.

Peripheral components of the cardiac innervation are also well characterized (reviewed by Fukuda *et al.* 2015; Habecker *et al.* 2016; Rajendran *et al.* 2019; Scalco *et al.* 2021). Baroreceptors, chemoreceptors and sensory afferent fibres, the cell bodies of which lie in the dorsal root ganglia and nodose ganglia, provide sensory feedback to allow cardiac activity to rapidly adapt to external stimuli. Preganglionic parasympathetic neurons project to the heart via the vagus nerve and form cholinergic synapses with the postganglionic neurons in the intracardiac ganglia located on the epicardial fat pads. Acetylcholine (ACh) released from postganglionic parasympathetic neurons activates M2 muscarinic receptors (M_2R) in the sinoatrial (SA) node, atrioventricular (AV) node, atria and, to a lesser extent, ventricles, in order to decrease heart rate (chronotropy) and conduction velocity (dromotropy). Sympathetic preganglionic neurons in the intermediolateral spinal cord receive cholinergic inputs from central premotor neurons and send cholinergic signals through the sympathetic chain to the nicotinic ACh receptors (nAChR) on the postganglionic neurons in the stellate ganglia and, to a lesser extent, T1–T3 thoracic ganglia. The postganglionic sympathetic neurons travel to the heart via the inferior cardiac nerve (iCN) and release noradrenaline (NA) onto β-adrenergic receptors (β_1-AR) in the SA node, AV node and cardiac myocytes to increase heart rate, conduction velocity, and contractility (inotropy) (Fig. 1). This general organization and

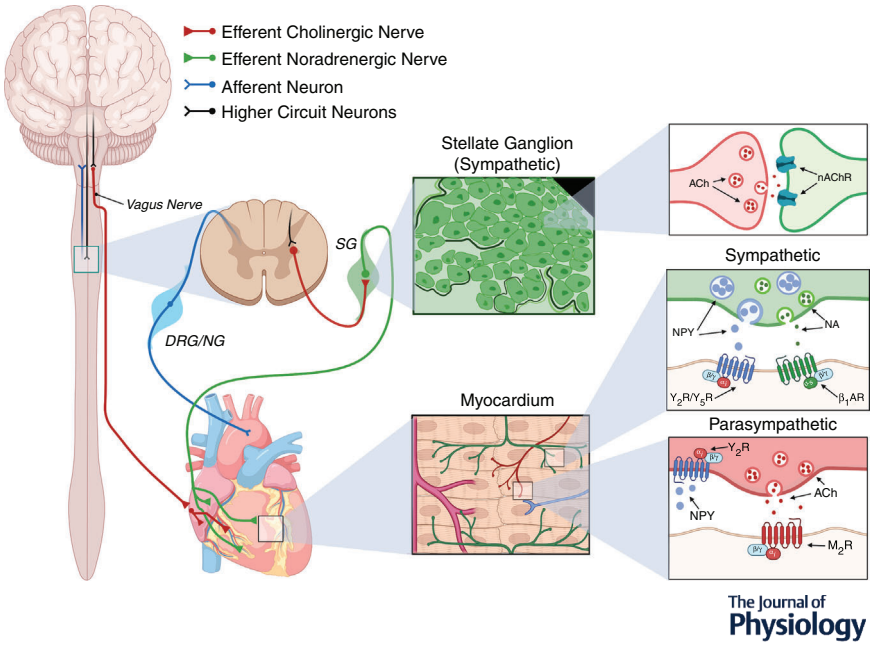

Figure 1. A schematic diagram illustrating the sympathetic and parasympathetic circuits involved in cardiac activity
Preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus send efferent cholinergic projections (red) via the vagus nerve to activate nicotinic acetylcholine receptors (nAChR) on postganglionic neurons in the intracardiac ganglia. ACh released from postganglionic parasympathetic neurons (red) activates M2 muscarinic receptors (M_2R) on node cells and cardiac myocytes. Sympathetic preganglionic neurons in the intermediolateral spinal cord (red) receive cholinergic inputs from sympathetic central premotor neurons and send cholinergic signals to the nAChR on postganglionic neurons in the stellate ganglia (SG) and T1–T3 sympathetic ganglia. The postganglionic sympathetic neurons (green) release noradrenaline onto β1-adrenergic receptors (β_1AR) of node cells and cardiac myocytes. Neuropeptide Y (NPY) is co-released from postganglionic sympathetic terminals to activate the Y2 and Y5 NPY receptors on myocytes (Y_2R and Y_5R, respectively). The parasympathetic terminals in the heart also express presynaptic Y_2R and are sensitive to NPY release from sympathetic terminals. Sensory afferent fibres in the heart (blue), baroreceptors and chemoreceptors provide sensory feedback via the vagal nerve, dorsal root ganglia (DRG) and nodose ganglia (NG) to allow cardiac activity to adapt rapidly to external stimuli.

neurochemistry is conserved across species. In humans and larger animals parasympathetic tone predominates in health, while sympathetic transmission prevails in smaller animals, including rodents (Fukuda *et al*. 2015; Habecker *et al*. 2016).

Intrinsic neural networks within the heart process and integrate these autonomic signals to control heart rate, cardiac conduction, and the force of contraction (reviewed by Ardell *et al*. 2016). The intrinsic cardiac nervous system is composed of sensory afferent fibres, extrinsic autonomic projections and interneurons within the local circuit. The cell bodies of intrinsic cardiac neurons lie within the intracardiac ganglia, which include post-ganglionic parasympathetic neurons. Intrinsic cardiac neurons transmit information within and between the intracardiac ganglia, and are the final site of sympathetic, parasympathetic and sensory integration for control of cardiac activity.

Neural control of the heart in disease

The cardiac reflexes that serve to maintain homeostasis are disrupted in many disease states, and are often characterized by increased sympathetic activity and decreased parasympathetic transmission (reviewed by Fukuda *et al*. 2015; Habecker *et al*. 2016; Rajendran *et al*. 2019). This autonomic imbalance contributes to many life-threatening cardiovascular pathologies including arrhythmia and sudden cardiac death. Decreased parasympathetic activity in the heart – which is identified clinically by decreased baroreflex sensitivity, heart rate variability, or heart rate recovery after exercise – correlates with increased risk of arrhythmias and death (La Rovere *et al*. 2001; Florea & Cohn, 2014; Herring *et al*. 2019).

Extensive studies carried out in animal models of cardiovascular disease reveal remodelling of cardiac neurocircuits at several functional and anatomical levels. Ischaemia or mechanical changes in the heart can activate sensory nerves that subsequently stimulate non-homeostatic sympatho-excitatory reflexes. Therefore, ablating cardiac sensory afferents in the heart can blunt the pathological increase in sympathetic outflow that normally follows cardiac damage and prevent progression of fibrosis (Wang *et al*. 2017). Likewise, central autonomic neurocircuits are remodelled in many disease states so that neurons within sympathetic circuits become hyperactive, while neurons involved in parasympathetic control exhibit decreased activity (Cauley *et al*. 2015). Excessive sympathetic transmission in the heart contributes to cardiac hypertrophy and fibrosis, and can trigger arrhythmias (Fukuda *et al*. 2015; Gardner *et al*. 2016; Habecker *et al*. 2016). Targeting the CNS to elevate cardiac parasympathetic transmission (Garrott *et al*. 2017) or prevent sympathetic over-activation (Wang *et al*. 2004) blunts the development of cardiac fibrosis in animal models of heart failure. However, decreasing sympathetic transmission in patients by targeting the CNS has proven ineffective in reducing arrhythmia risk (Florea & Cohn, 2014). In contrast, peripheral disruption of sensory or sympathetic transmission prevents arrhythmias and prolongs life (Vaseghi *et al*. 2017a; Herring *et al*. 2019; Dusi *et al*. 2021), suggesting that dysfunction in peripheral neurocircuits plays an important and distinct role in pathophysiology.

Neural remodelling in disease

Several distinct types of peripheral neural remodelling have been identified in response to injury and disease. These include changes in neuronal excitability, altered neurotransmitter or neuropeptide production, and hyperinnervation (increased nerve density) or denervation (decreased nerve density) of cardiac tissue. Autonomic remodelling in heart failure with reduced ejection fraction, for example, includes increased excitability in sympathetic stellate ganglia (Han *et al*. 2012), hyperinnervation of the myocardium (Cao *et al*. 2000), altered firing frequencies of sensory afferents (Wang *et al*. 2017), and disruption of firing patterns and connections within intracardiac ganglia (Vaseghi *et al*. 2017b). These distinct types of neural remodelling have been best characterized in cardiac sympathetic and parasympathetic neurons.

Sympathetic remodelling

Increased neural excitability. Sympathetic hyperactivity elevates plasma levels of NA and its metabolite, dihydroxyphenylglycol, which are associated with poor patient outcomes in heart failure with either preserved or reduced ejection fraction (Denfeld *et al*. 2019; Grassi *et al*. 2019). Many studies have tried to elucidate the basis for enhanced sympathetic transmission and NA spillover in the failing heart (reviewed by Grassi *et al*. 2019). Decreased NA reuptake contributes to the build-up of extracellular NA, but other factors are also involved. Postganglionic sympathetic neurons become hyperactive in cardiovascular disease, and that increased activity corresponds with increased cell body size, enhanced synaptic transmission within stellate ganglia, and increased NA release to cardiac myocytes in animals and humans alike (Ajijola *et al*. 2012; Han *et al*. 2012). Downregulation of the M current, changes in neuronal cyclic nucleotide signalling, and decreased nitric oxide synthase (nNOS) in cardiovascular disease also drive excess NA release by increasing intracellular Ca^{2+} and intrinsic neuronal excitability (Bardsley & Paterson, 2020; Davis *et al*. 2020).

Altered neurotransmitter or neuropeptide production. Sympathetic neurons also exhibit changes in neuropeptide and neurotransmitter expression in addition to excessive noradrenergic transmission in cardiovascular disease (Fig. 2). Recent studies revealed that diseased neurons release adrenaline along with NA, activating additional populations of β-AR (Bardsley *et al.* 2018). Clinical studies have identified enhanced neuropeptide Y (NPY) release in patients with myocardial infarction and heart failure with reduced and preserved ejection fraction, which may lead to microvascular constriction and ventricular arrhythmias (Ajijola *et al.* 2019; Kalla *et al.* 2020). NPY is released from sympathetic neurons, acting on NPY receptors in vascular smooth muscle (Y_1R) and cardiac myocytes (Y_2R, Y_5R) (Tan *et al.* 2018). New data indicate that a subset of cardiac parasympathetic neurons may also express NPY, but the functional consequences are not clear (Hanna *et al.* 2021). NPY and other neuropeptides inhibit release of ACh from cardiac parasympathetic nerve terminals via Y_2R in addition to effects on the heart and vasculature (Fig. 1) (Herring *et al.* 2008;Tan *et al.* 2018). The adverse effects of elevated NPY may explain why many patients on β-AR blockers receive additional benefits from stellate ganglionectomy (Dusi *et al.* 2021). Surprisingly, peripheral sympathetic neurons also undergo cholinergic transdifferentiation in heart failure with reduced ejection fraction and myocardial infarction, synthesizing and releasing ACh in addition to NA (Kanazawa *et al.* 2010; Olivas *et al.* 2016). The functional impact of cholinergic sympathetic transmission is not well understood, but co-release of ACh seems to reduce the heterogeneity of action potential duration without impacting contractility (Wang *et al.* 2020).

Changes in nerve distribution. In addition to changes in neural excitability and neurotransmission, the distribution and density of sympathetic nerves is commonly altered in diseases that affect the heart (reviewed by Fukuda *et al.* 2015; Gardner *et al.* 2016). Areas of ventricular hyperinnervation have been identified in several pathophysiological conditions including myocardial infarction, heart failure, spinal cord injury and diet-induced obesity. Regional deficits in cardiac sympathetic transmission, identified in patients by imaging the uptake of labelled NA transporter substrates, are also present in many pathologies including heart failure, myocardial infarction, diabetic neuropathy and Parkinson's disease (Fukuda *et al.* 2015; Gardner *et al.* 2016). Regions of denervation and hyperinnervation can be present in the same heart, and the heterogeneity of sympathetic nerve distribution contributes to cardiac arrhythmias (Herring *et al.* 2019).

Nerve growth factor. Many of the injury-induced alterations in cardiac nerves are driven by changes in nerve growth factor (NGF). Increased cardiac NGF after myocardial infarction and in compensated cardiac hypertrophy contributes to sympathetic hyperinnervation, while decreased NGF in decompensated heart failure and diabetes contributes to sympathetic denervation, impaired NA reuptake, and loss of afferent nerve function (Fukuda *et al.* 2015; Habecker *et al.* 2016). Retrograde

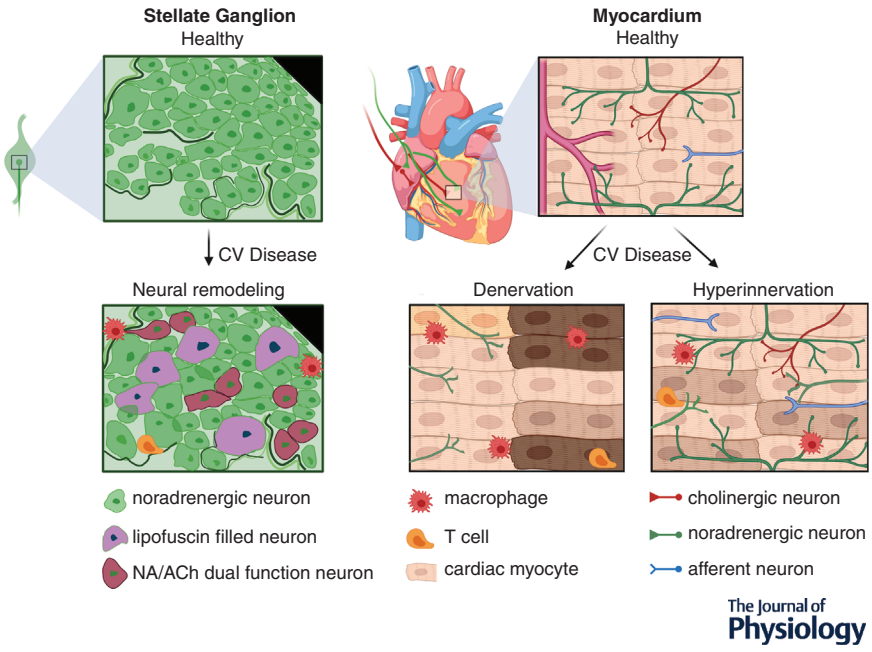

Figure 2. A schematic diagram illustrating changes in peripheral neurons in cardiac injury and disease
In the stellate ganglion (left) inflammatory T-cells and macrophages infiltrate the stellate ganglion, and inflammatory cytokine expression stimulates production of ACh in addition to NA. The size and activity of cardiac sympathetic neurons also increases in disease, with lipofuscin accumulation occurring in many cells. In the myocardium (right) cardiac injury and disease are associated with the infiltration of macrophages and T-cells and disrupt the distribution and density of nerves, resulting in areas of denervation and hyperinnervation.

signalling by cardiac NGF contributes to morphological changes in stellate neurons during disease (Lujan *et al.* 2012), and NGF synthesis by parasympathetic neurons is implicated in establishing and maintaining synaptic interactions between parasympathetic and sympathetic axons (Hasan & Smith, 2000).

Parasympathetic remodelling

Compared to the pathophysiological modulation of sympathetic activity, far less is known about the disruption of peripheral parasympathetic activity in cardiac patients. The location of postganglionic parasympathetic neurons and the diverse neural populations of the intracardiac ganglia make *in vivo* assessment of peripheral parasympathetic activity difficult. As such, direct analysis of parasympathetic activity is restricted to single nerve fibre recordings (Cerati & Schwartz, 1991). This evidence and studies utilizing indirect measures of parasympathetic activity, such as heart rate variability analysis and baroreflex sensitivity, all suggest that parasympathetic activity is depressed following myocardial infarction, in heart failure with preserved and reduced ejection fraction, and in metabolic disease (Binkley *et al.* 1991; Florea & Cohn, 2014; Wulsin *et al.* 2015).

Decreased neural activity. Clinical studies indicate that the markers of reduced vagal activity, including depressed baroreflex sensitivity and heart rate variability, are strong predictors of cardiac mortality after myocardial infarction (La Rovere *et al.* 2001) and in heart failure with reduced or preserved ejection fraction (Florea & Cohn, 2014). Likewise, *in vivo* recordings of parasympathetic neurons in the intracardiac ganglia with multielectrode arrays indicate that neural activity is significantly reduced following myocardial infarction compared with healthy hearts (Vaseghi *et al.* 2017b). These data suggest that myocardial infarction disrupts parasympathetic activity via central mechanisms relayed to the heart via the vagus nerve. Reduced parasympathetic activity is also observed in metabolic disorders such as type II diabetes, where it predicts the development of cardiovascular disease and early mortality (Wulsin *et al.* 2015).

Structural and neurochemical plasticity. The neurochemical phenotype and structural characteristics of intracardiac neurons, which include postganglionic parasympathetic neurons, are altered in cardiovascular disease. The expression of choline acetyltransferase in intracardiac neurons of porcine hearts is reduced significantly after myocardial infarction (Rajendran *et al.* 2016), and failing canine hearts exhibit reduced acetylcholinesterase activity and altered distribution and composition of muscarinic receptors (Dunlap *et al.* 2003). Vasoactive intestinal peptide is upregulated in the intracardiac ganglia following myocardial infarction, which may exert chronotropic and inotropic actions to compensate for disrupted cardiac activity (Rajendran *et al.* 2016). These neurons undergo structural changes in human cardiovascular disease, exhibiting increased size compared with control neurons as well as cytoplasmic inclusions and lipofuscins, which are markers for neural degeneration (Hopkins *et al.* 2000). These data suggest that cardiac pathologies disrupt parasympathetic transmission peripherally as well as centrally.

Inflammation and neural remodelling

Cardiovascular diseases are strongly associated with peripheral and central inflammation. Within the CNS, neural–immune interactions contribute to the pathological rise in sympathetic activity (reviewed by Díaz *et al.* 2020). Immune cells also contribute to injury-induced changes in peripheral autonomic nerves. For example, macrophage infiltration of cardiac tissue after ischaemic injury stimulates nerve sprouting and hyperinnervation through local release of NGF (Wernli *et al.* 2009). Elevated proinflammatory cytokines including leukaemia inhibitory factor and interleukin-6 also contribute to sympathetic nerve sprouting, as removal of neuronal gp130 prevents timely regeneration (Pellegrino & Habecker, 2013). Increased cytokine-dependent gp130-signalling in myocardial infarction and heart failure also alters neurotransmitter production in cardiac sympathetic neurons by inducing the expression of genes associated with cholinergic transmission (Kanazawa *et al.* 2010; Olivas *et al.* 2016). This indicates that cholinergic transdifferentiation of sympathetic nerves occurs as a direct result of injury-induced inflammation, and raises the possibility that cholinergic sympathetic transdifferentiation is present in other pathologies with sustained inflammation.

Ganglionic inflammation and the role of peripheral glia. Cardiac injury leads to infiltration of immune cells such as macrophages and T-cells in autonomic ganglia in addition to the heart, and oxidative stress leads to neuronal accumulation of lipofuscin, a marker for cellular damage and ageing (James *et al.* 1979; Ajijola *et al.* 2017). Elevated proinflammatory cytokines and immune cell infiltration within peripheral ganglia is also associated with changes in glial phenotype, characterized by increased expression of the glial activation marker, glial fibrillary acid protein (Fig. 3). Injury-induced inflammation appears to change the signalling properties between glia in autonomic and sensory ganglia by upregulating the expression of gap junctions (reviewed by Hanani & Spray, 2020). Satellite glial cells (SGCs) form glial networks through gap

junctions that allow for glia-to-glia communication via electrical impulses or the transport of small molecules. Increasing gap junction number enhances the functional coupling of glial networks. SGCs also express neurotransmitter transporters, similar to astrocytes in the CNS, and can secrete neuroactive substances such as proinflammatory cytokines and gliotransmitters (Hanani & Spray, 2020). This suggests that SGCs may be capable of sensing and responding to cardiac damage and other pathophysiological conditions, and may contribute to the hyperexcitability of cardiac sensory and sympathetic neurons. Consistent with this idea, adding SGCs to cultured sympathetic neurons *in vitro* increases neuronal excitability (Enes *et al.* 2020). The signalling mechanisms involved in glial modulation of neuronal activity in the periphery are not well understood, but in the CNS, inflammation disrupts direct glia–neuron signalling in a manner that subsequently dysregulates synaptic transmission and neural excitability (Díaz *et al.* 2020). In total, ganglionic inflammation may be an important factor in the dysregulation of autonomic cardiac neurocircuits in pathophysiology.

Therapeutics targeting cardiac innervation

Clinical strategies that aim to restore autonomic balance in disease or after cardiac injury include both pharmacological and neuromodulatory techniques (reviewed by Florea & Cohn, 2014; Grassi *et al.* 2019; Herring *et al.* 2019; Hadaya & Ardell, 2020). Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and β-AR antagonists (i.e.

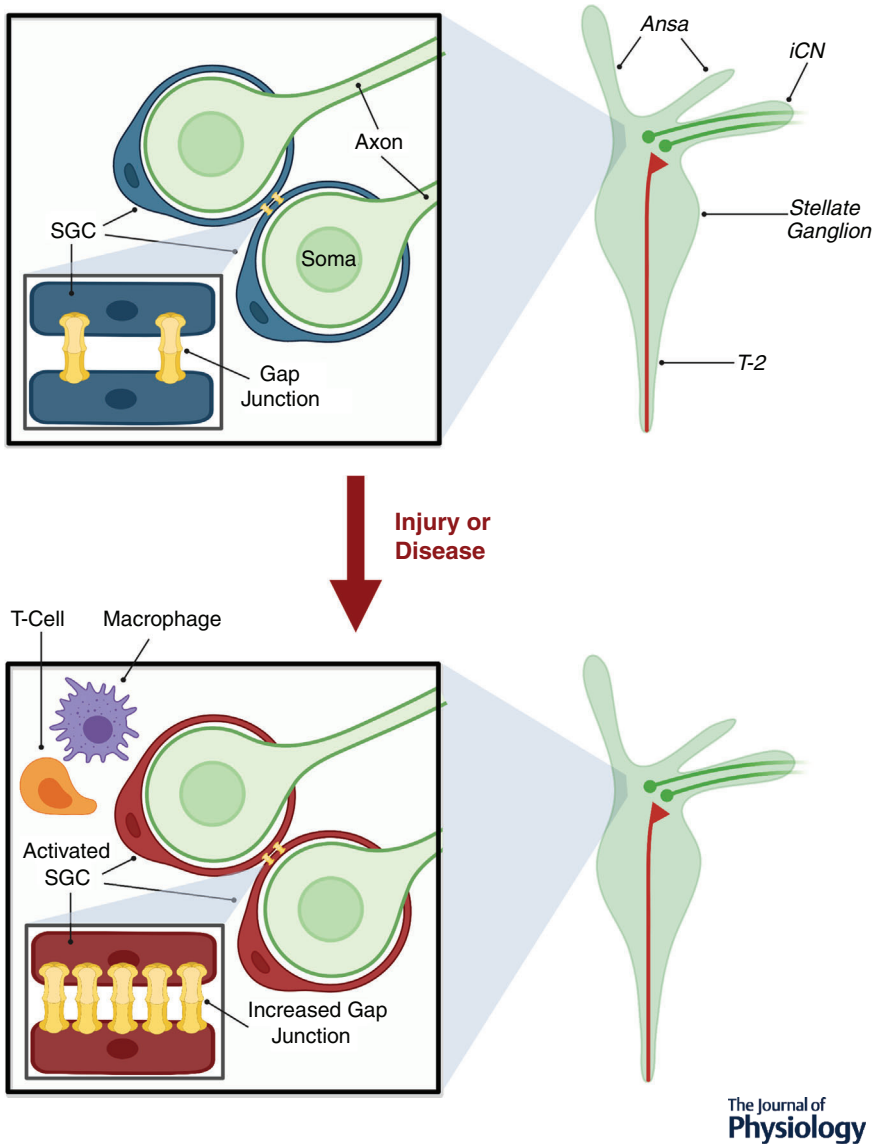

Figure 3. A schematic diagram of injury- and disease-induced changes in stellate ganglion
Under physiological conditions (top), postganglionic sympathetic neurons are completely encapsulated by satellite glial cells (SGCs). SGCs form glial networks through the expression of gap junctions. After cardiac injury or disease (bottom), inflammatory cells including macrophages and T-cells infiltrate the ganglia and may contribute to the activation of SGCs and the upregulation of glial fibrillary acid protein. Gap junction expression is also upregulated after injury and disease, increasing the signalling and communication throughout glial networks.

beta blockers) are frequently prescribed to cardiac patients in order to push autonomic balance towards homeostasis. For cardiac patients that are resistant to pharmacological therapies, non-pharmacological techniques have also received attention for the treatment of autonomic dysfunction in cardiac patients. These include vagal nerve stimulation, spinal cord stimulation, renal denervation and surgical stellate ganglionectomy. Trials of these interventions have generated mixed results in many cases (Herring *et al.* 2019; Hadaya & Ardell, 2020), but sympathetic denervation via surgical stellate ganglionectomy has consistently decreased arrhythmias and prolonged life (Vaseghi *et al.* 2017a). Future studies aimed at elucidating the signalling mechanisms involved in sympathetic hyperactivity and the disruption of stellate ganglion neurons may identify novel and less invasive therapeutic targets for the treatment of autonomic cardiac dysfunction.

Conclusions

Neural control of cardiac function involves the integration of sensory, sympathetic and parasympathetic signalling with intrinsic cardiac neurocircuits to allow for the rapid regulation of cardiac activity in response to constantly changing stimuli. The balance of sympathetic and parasympathetic activity is disrupted in many disease states, tipping this sensitive equilibrium towards sympathetic hyperactivity and parasympathetic withdrawal and predisposing patients to cardiac arrhythmias and sudden cardiac death (Fig. 4). Although cardiovascular disease dysregulates cardiac autonomic activity at several functional and anatomical levels, changes in peripheral sympathetic transmission play an important role in disease progression and poor patient outcomes. The mechanisms that trigger and sustain increased sympathetic activity or decreased

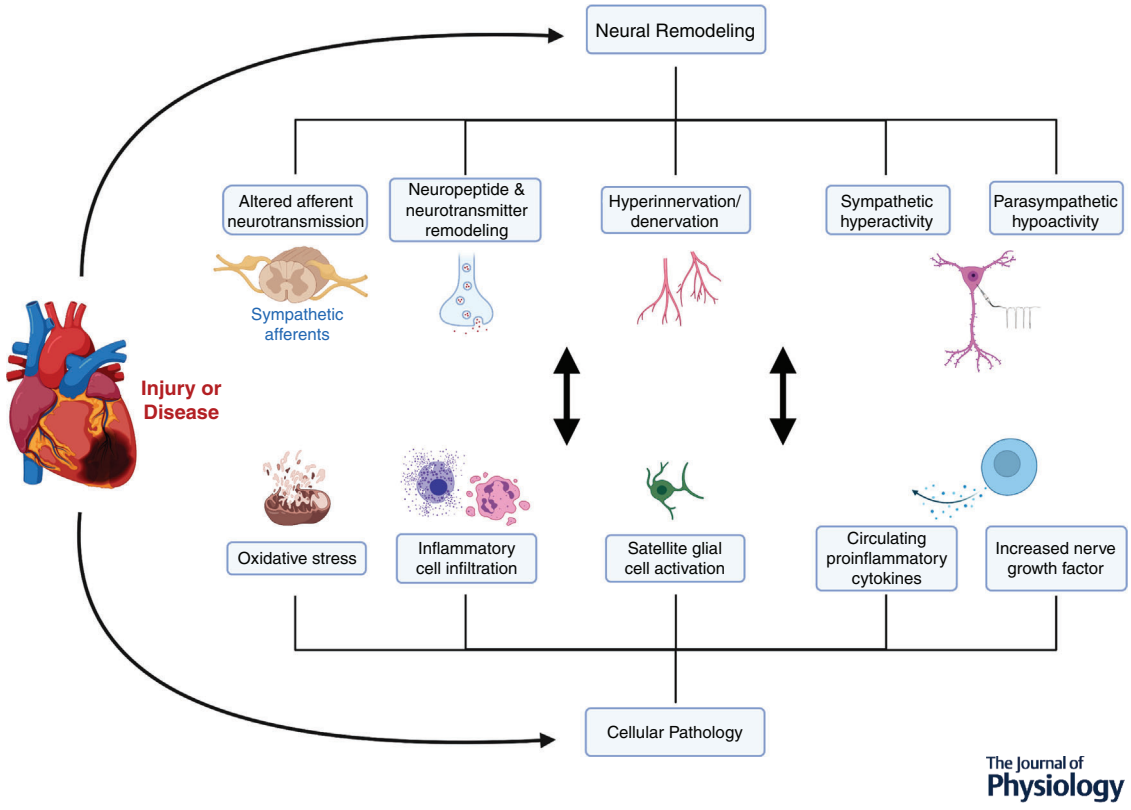

Figure 4. Summary diagram illustrating the neural remodelling (top) and cellular pathologies (bottom) observed in disease or following cardiac injury
Neural control of cardiac function involves the integration of sensory (afferent), sympathetic and parasympathetic neurotransmission, tipping the equilibrium toward sympathetic hyperactivity. Cardiac injury and disease is associated with several cellular pathologies including oxidative stress, infiltration of inflammatory cells to the myocardium and peripheral ganglia, elevation of proinflammatory cytokines and nerve growth factor, and activation of satellite glial cells. These contribute to the neural remodelling that occurs in disease: altered afferent neurotransmission, neuropeptide and neurotransmitter remodelling, changes in nerve density including hyperinnervation and denervation, as well as sympathetic hyperactivity and reduced parasympathetic transmission.

parasympathetic activity are not fully understood, but inflammation appears to be a key component of autonomic dysfunction in disease. Further studies are required to elucidate the role of systemic inflammation and tissue-specific inflammation in the heart and vasculature, and the dysregulation of neural activity in peripheral ganglia (sympathetic, parasympathetic and sensory). Understanding how disease- and injury-induced inflammation leads to disruption of neural cardiac control may identify novel targets for intervention and improve therapeutic strategies to improve health outcomes.

References

Ajijola OA, Chatterjee NA, Gonzales MJ, Gornbein J, Liu K, Li D, Paterson DJ, Shivkumar K, Singh JP & Herring N (2019). Coronary sinus neuropeptide Y levels and adverse outcomes in patients with stable chronic heart failure. *JAMA Cardiol* **5**, 318.

Ajijola OA, Hoover DB, Simerly TM, Brown TC, Yanagawa J, Biniwale RM, Lee JM, Sadeghi A, Khanlou N, Ardell JL & Shivkumar K (2017). Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. *JCI Insight* **2**, e94715.

Ajijola OA, Wisco JJ, Lambert HW, Mahajan A, Stark E, Fishbein MC & Shivkumar K (2012). Extracardiac neural remodeling in humans with cardiomyopathy. *Circ Arrhythm Electrophysiol* **5**, 1010–1116.

Ardell JL, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, Herring N, O'Leary DS, Sabbah HN, Schultz HD, Sunagawa K & Zucker IH (2016). Translational neurocardiology: preclinical models and cardioneural integrative aspects. *J Physiol* **594**, 3877–3909.

Bardsley EN, Davis H, Buckler KJ & Paterson DJ (2018). Neurotransmitter switching coupled to beta-adrenergic signaling in sympathetic neurons in prehypertensive states. *Hypertension (Dallas, Tex : 1979)* **71**, 1226–1238.

Bardsley EN & Paterson DJ (2020). Neurocardiac regulation: from cardiac mechanisms to novel therapeutic approaches. *J. Physiol* **598**, 2957–2976.

Binkley PF, Nunziata E, Haas GJ, Nelson SD & Cody RJ (1991). Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol* **18**, 464–472.

Cao JM, Fishbein MC, Han JB, Lai WW, Lai AC, Wu TJ, Czer L, Wolf PL, Denton TA, Shintaku IP, Chen PS & Chen LS (2000). Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* **101**, 1960–1969.

Cauley E, Wang X, Dyavanapalli J, Sun K, Garrott K, Kuzmiak-Glancy S, Kay MW & Mendelowitz D (2015). Neurotransmission to parasympathetic cardiac vagal neurons in the brain stem is altered with left ventricular hypertrophy-induced heart failure. *Am J Physiol Heart Circ Physiol* **309**, H1281–H1287.

Cerati D & Schwartz PJ (1991). Single cardiac vagal fiber activity, acute myocardial ischemia, and risk for sudden death. *Circ Res* **69**, 1389–1401.

Coote JH & Spyer KM (2018). Central control of autonomic function. *Brain Neurosci Adv* **2**, 239821281881201.

Dampney RAL (2016). Central neural control of the cardiovascular system: current perspectives. *Adv Physiol Educ* **40**, 283–296.

Davis H, Herring N & Paterson DJ (2020). Downregulation of M current is coupled to membrane excitability in sympathetic neurons before the onset of hypertension. *Hypertension (Dallas, Tex : 1979)* **76**, 1915–1923.

Denfeld QE, Lee CS, Woodward WR, Hiatt SO, Mudd JO & Habecker BA (2019). Sympathetic markers are different between clinical responders and nonresponders after left ventricular assist device implantation. *J Cardiovasc Nurs* **34**, E1–E10.

Díaz HS, Toledo C, Andrade DC, Marcus NJ & Del Rio R (2020). Neuroinflammation in heart failure: new insights for an old disease. *J Physiol* **598**, 33–59.

Dunlap ME, Bibevski S, Rosenberry TL & Ernsberger P (2003). Mechanisms of altered vagal control in heart failure: influence of muscarinic receptors and acetylcholinesterase activity. *Am J Physiol Heart Circ Physiol* **285**, H1632–H1640.

Dusi V, Gornbein J, Do DH, Sorg JM, Khakpour H, Krokhaleva Y, Ajijola OA, Macias C, Bradfield JS, Buch E, Fujimura OA, Boyle NG, Yanagawa J, Lee JM, Shivkumar K & Vaseghi M (2021). Arrhythmic risk profile and outcomes of patients undergoing cardiac sympathetic denervation for recurrent monomorphic ventricular tachycardia after ablation. *J Am Heart Assoc* **10**, e018371.

Enes J, Haburčák M, Sona S, Gerard N, Mitchell AC, Fu W & Birren SJ (2020). Satellite glial cells modulate cholinergic transmission between sympathetic neurons. *PLoS One* **15**, e0218643–e0218643.

Florea VG & Cohn JN (2014). The autonomic nervous system and heart failure. *Circ Res* **114**, 1815–1826.

Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K (2015). Cardiac innervation and sudden cardiac death. *Circ Res* **116**, 2005–2019.

Gardner RT, Ripplinger CM, Myles RC & Habecker BA (2016). Molecular mechanisms of sympathetic remodeling and arrhythmias. *Circ Arrhythm Electrophysiol* **9**, e001359.

Garrott K, Dyavanapalli J, Cauley E, Dwyer MK, Kuzmiak-Glancy S, Wang X, Mendelowitz D & Kay MW (2017). Chronic activation of hypothalamic oxytocin neurons improves cardiac function during left ventricular hypertrophy-induced heart failure. *Cardiovasc Res* **113**, 1318–1328.

Grassi G, Quarti-Trevano F & Esler MD (2019). Sympathetic activation in congestive heart failure: an updated overview. *Heart Fail Rev*. https://doi.org/10.1007/s10741-10019-09901-10742.

Habecker BA, Anderson ME, Birren SJ, Fukuda K, Herring N, Hoover DB, Kanazawa H, Paterson DJ & Ripplinger CM (2016). Molecular and cellular neurocardiology: development, and cellular and molecular adaptations to heart disease. *J Physiol* **594**, 3853–3875.

Hadaya J & Ardell JL (2020). Autonomic modulation for cardiovascular disease. *Front Physiol* **11**, 617459.

Han S, Kobayashi K, Joung B, Piccirillo G, Maruyama M, Vinters HV, March K, Lin SF, Shen C, Fishbein MC, Chen PS & Chen LS (2012). Electroanatomic remodeling of the left stellate ganglion after myocardial infarction. *J Am Coll Cardiol* **59**, 954–961.

Hanani M & Spray DC (2020). Emerging importance of satellite glia in nervous system function and dysfunction. *Nat Rev Neurosci* **21**, 485–498.

Hanna P, Dacey MJ, Brennan J, Moss A, Robbins S, Achanta S, Biscola NP, Swid MA, Rajendran PS, Mori S, Hadaya JE, Smith EH, Peirce SG, Chen J, Havton LA, Cheng ZJ, Vadigepalli R, Schwaber J, Lux RL, Efimov I, Tompkins JD, Hoover DB, Ardell JL & Shivkumar K (2021). Innervation and neuronal control of the mammalian sinoatrial node a comprehensive atlas. *Circ Res* **128**, 1279–1296.

Hasan W & Smith PG (2000). Nerve growth factor expression in parasympathetic neurons: regulation by sympathetic innervation. *Eur J Neurosci* **12**, 4391–4397.

Herring N, Kalla M & Paterson DJ (2019). The autonomic nervous system and cardiac arrhythmias: current concepts and emerging therapies. *Nat Rev Cardiol* **16**, 707–726.

Herring N, Lokale MN, Danson EJ, Heaton DA & Paterson DJ (2008). Neuropeptide Y reduces acetylcholine release and vagal bradycardia via a Y2 receptor-mediated, protein kinase C-dependent pathway. *J Mol Cell Cardiol* **44**, 477–485.

Hopkins DA, Macdonald SE, Murphy DA & Armour JA (2000). Pathology of intrinsic cardiac neurons from ischemic human hearts. *Anat Rec* **259**, 424–436.

James TN, Zipes DP, Finegan RE, Eisele JW & Carter JE (1979). Cardiac ganglionitis associated with sudden unexpected death. *Ann Intern Med* **91**, 727–730.

Kalla M, Hao G, Tapoulal N, Tomek J, Liu K, Woodward L, Oxford Acute Myocardial Infarction S, Dall'Armellina E, Banning AP, Choudhury RP, Neubauer S, Kharbanda RK, Channon KM, Ajijola OA, Shivkumar K, Paterson DJ & Herring N (2020). The cardiac sympathetic co-transmitter neuropeptide Y is pro-arrhythmic following ST-elevation myocardial infarction despite beta-blockade. *Eur Heart J* **41**, 2168–2179.

Kanazawa H, Ieda M, Kimura K, Arai T, Kawaguchi-Manabe H, Matsuhashi T, Endo J, Sano M, Kawakami T, Kimura T, Monkawa T, Hayashi M, Iwanami A, Okano H, Okada Y, Ishibashi-Ueda H, Ogawa S & Fukuda K (2010). Heart failure causes cholinergic transdifferentiation of cardiac sympathetic nerves via gp130-signaling cytokines in rodents. *J Clin Invest* **120**, 408–421.

La Rovere MT, Pinna GD, Hohnloser SH, Marcus FI, Mortara A, Nohara R, Bigger JT, Jr., Camm AJ & Schwartz PJ (2001). Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation* **103**, 2072–2077.

Lujan HL, Janbaih H & DiCarlo SE (2012). Dynamic interaction between the heart and its sympathetic innervation following T5 spinal cord transection. *J Appl Physiol (1985)* **113**, 1332–1341.

Olivas A, Gardner RT, Wang L, Ripplinger CM, Woodward WR & Habecker BA (2016). Myocardial infarction causes transient cholinergic transdifferentiation of cardiac sympathetic nerves via gp130. *J Neurosci* **36**, 479–488.

Pellegrino MJ & Habecker BA (2013). STAT3 integrates cytokine and neurotrophin signals to promote sympathetic axon regeneration. *Mol Cell Neurosci* **56**, 272–282.

Rajendran PS, Challis RC, Fowlkes CC, Hanna P, Tompkins JD, Jordan MC, Hiyari S, Gabris-Weber BA, Greenbaum A, Chan KY, Deverman BE, Munzberg H, Ardell JL, Salama G, Gradinaru V & Shivkumar K (2019). Identification of peripheral neural circuits that regulate heart rate using optogenetic and viral vector strategies. *Nat Commun* **10**, 1944.

Rajendran PS, Nakamura K, Ajijola OA, Vaseghi M, Armour JA, Ardell JL & Shivkumar K (2016). Myocardial infarction induces structural and functional remodelling of the intrinsic cardiac nervous system. *J Physiol* **594**, 321–341.

Scalco A, Moro N, Mongillo M & Zaglia T (2021). Neurohumoral cardiac regulation: optogenetics gets into the groove. *Front Physiol* **12**, 726895.

Tan CMJ, Green P, Tapoulal N, Lewandowski AJ, Leeson P & Herring N (2018). The role of neuropeptide Y in cardiovascular health and disease. *Front Physiol* **9**, 1281.

Vaseghi M, Barwad P, Malavassi Corrales FJ, Tandri H, Mathuria N, Shah R, Sorg JM, Gima J, Mandal K, Saenz Morales LC, Lokhandwala Y & Shivkumar K (2017*a*). Cardiac sympathetic denervation for refractory ventricular arrhythmias. *J Am Coll Cardiol* **69**, 3070–3080.

Vaseghi M, Salavatian S, Rajendran PS, Yagishita D, Woodward WR, Hamon D, Yamakawa K, Irie T, Habecker BA & Shivkumar K (2017*b*). Parasympathetic dysfunction and antiarrhythmic effect of vagal nerve stimulation following myocardial infarction. *JCI Insight* **2**, e86715.

Wang H, Huang BS, Ganten D & Leenen FH (2004). Prevention of sympathetic and cardiac dysfunction after myocardial infarction in transgenic rats deficient in brain angiotensinogen. *Circ Res* **94**, 843.

Wang HJ, Rozanski GJ & Zucker IH (2017). Cardiac sympathetic afferent reflex control of cardiac function in normal and chronic heart failure states. *J Physiol* **595**, 2519–2534.

Wang L, Olivas A, Francis Stuart SD, Tapa S, Blake MR, Woodward WR, Habecker BA & Ripplinger CM (2020). Cardiac sympathetic nerve transdifferentiation reduces action potential heterogeneity after myocardial infarction. *Am J Physiol Heart Circ Physiol* **318**, H558–H565.

Wernli G, Hasan W, Bhattacherjee A, van Rooijen N & Smith PG (2009). Macrophage depletion suppresses sympathetic hyperinnervation following myocardial infarction. *Basic Res Cardiol* **104**, 681–693.

Wulsin LR, Horn PS, Perry JL, Massaro J & D'Agostino R (2015). Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality autonomic imbalance predicts CVD, DM, mortality. *J Clin Endocrinol Metab* 100, 2443-2448.

Additional information

Competing interests

The authors have nothing to declare.

Author contributions

C.C., J.S. and B.H. all contributed to drafting the work and revising it critically for important intellectual content. All authors 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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