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Autonomic Nervous System and Neurocardiac Physiopathology

John G. Kingma, Denys Simard and
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Abstract

The autonomic nervous system regulates multiple physiological functions; how distinct neurons in peripheral autonomic and intrathoracic ganglia communicate remains to be established. Increasing focus is being paid to functionality of the neurocardiac axis and crosstalk between the intrinsic nervous system and diverse organ systems. Current findings indicate that progression of cardiovascular disease comprises peripheral and central aspects of the cardiac nervous system hierarchy. Indeed, autonomic neuronal dysfunction is known to participate in arrhythmogenesis and sudden cardiac death; diverse interventions (pharmacological, non-pharmacological) that affect neuronal remodeling in the heart following injury caused by cardiovascular disease (congestive heart failure, etc.) or acute myocardial infarction are being investigated. Herein we examine recent findings from clinical and animal studies on the role of the intrinsic cardiac nervous system on regulation of myocardial perfusion and the consequences of cardiac injury. We also discuss different interventions that target the autonomic nervous system, stimulate neuronal remodeling and adaptation, and thereby optimize patient outcomes.

Keywords: autonomic nervous system, sympathetic, parasympathetic nerves, intrinsic cardiac neurons, intrinsic cardiac nervous system, ischemia, arrhythmias

1. Introduction

Physiological functions (i.e. muscle contraction, glandular function, visceral activity, nerve impulses, etc.) of the body are controlled by the autonomic nervous system (ANS). Innervation to the heart is consistent among species [1–3]; the ANS comprises central, intrathoracic extracardiac and intrinsic cardiac components (see review by Hanna et al. [4]). The sympathetic and parasympathetic systems interact to stimulate energy expenditure under conditions of stress or return the

body to a restful state; these systems comprise pathways that include preganglionic and post-ganglionic neurons (activated by endogenous chemical neurotransmitters). Increasing attention focuses on the complex anatomy and function of the cardiac neuraxis; how diverse populations of neurons in peripheral autonomic and intrathoracic ganglia communicate with each other and between different organ systems remains the subject of ongoing investigation. Treatment strategies that modulate the ANS are being developed and tested in the setting of cardiac dysfunction, arrhythmias and sudden death with the objective of stimulating or maintaining cardiovascular function. Improved mechanistic understanding of changes that occur within the nervous system hierarchy during pathogenesis of cardiac disease is therefore essential. This chapter examines current scientific literature on the effects of ischemia on the cardiac nervous system; the role of intrinsic cardiac neurons on regulation of myocardial blood flow, cardiac function, pathogenesis of nerve and myocardial tissue injury is discussed. For this review, clinical and basic science reports were searched on MEDLINE, Google Scholar and PubMed with the keywords intrinsic cardiac nervous system (ICNS), ischemia, reperfusion, cellular protection, myocardium, nerves and combinations thereof. In addition, we referred to data from our own research.

2. Cardiac nervous system

The sympathetic (adrenergic) component of the ANS stimulates cardiac conduction and myocardial cells; on the other hand, the parasympathetic (cholinergic) nervous system exerts an inhibitory influence [5, 6]. Regulation of cardiac performance by the ANS involves modulation of heart rate (positive chronotropy), increases in cardiac contractility (positive inotropy) and cardiac relaxation (positive lusitropy), decreased venous capacitance plus constriction of resistance and cutaneous vessels [7].

Sympathetic cardiac nerves originate from stellate, superior, middle cervical and thoracic ganglia [8]; postganglionic sympathetic neurons project efferent axons to the heart [9]. Parasympathetic nerves develop from the cardiac component of the cranial neural crest; pre-ganglionic neurons access to the heart occurs via the vagus nerves [10, 11]. Cardiac ganglia are located in epicardial fat, in ganglionated plexi adjacent to the major cardiac vessels and in the ventricular wall [12–14]. ANS neurons are classified by chemical phenotyping; cholinergic and adrenergic populations of ganglionic cardiac neurons are readily found in cardiac ganglia [15–17]. Sensory neurons, interneurons and sensory fibers that develop from the *nucleus ambiguus* [18–20] likely play a role in pathogenesis of cardiac disease. In fact, activation of the neuroendocrine system is considered central to pathogenesis of cardiac disease; excess sympathetic activation promotes cardiovascular dysfunction, arrhythmias and sudden death [21]. Of note, is that visualization of the ICNS and the presence of interneuron connections is particularly challenging [22–25]; however, several immune histochemical techniques which target specific neurotransmitters within parasympathetic and sympathetic neurons have been particularly successful [26–30]. Neuroimaging techniques, cardioneural optical mapping and optogenetics are also being used to define the complex anatomy of the cardiac nervous system in animals and living humans to evaluate the role of the ANS in normal cardiac function as well as pathogenesis of cardiac disease [4, 31–33].

3. Vasoregulation

Arteries normally respond to humoral, metabolic, mechanical and neural stimulation; local metabolic control occurs secondarily to myocardial metabolic change [34, 35]. In the heart, blood flow across the ventricular wall is precisely coordinated to metabolic requirements via adjustments in vessel tone; flow is therefore independent of external physical factors since metabolism is the ultimate determinant of regional perfusion over the operative range of autoregulation [36–38]. The ANS contributes to regulation of myocardial blood flow; sympathetic nerve stimulation produces a biphasic response, which trends to coronary dilatation resulting from increases in myocardial oxygen demand as well as perfusion pressure [39, 40]. Neuropeptide chemicals elevate local catecholamine levels that modulate cardiac dynamics and indirectly increase blood flow across the left ventricular wall [40–42]. In dogs, with an intact cardiac nervous system, we documented significant increases in myocardial blood flow following application of nicotine or bradykinin to selected ganglionated plexi on the heart [40]; stimulation of nicotine sensitive neurons increases cardiac metabolic demand (i.e. higher heart rate and LV systolic pressure) but stimulation with bradykinin produces a similar result without affecting LV pressure. On the other hand, Vergroesen et al. documented that intact cardiac nerves were not essential for regulation of coronary blood flow [43]; however, they suggested that cardiac nerves essentially alter the speed of response of the coronary vascular bed to changes in heart rate and perfusion pressure. The cardiac nervous reflexes thought to be responsible for these effects has not been established but diverse cardiac afferent fibers and receptor subtypes (i.e. ventricular, coronary artery) have been studied.

Stimulation of ventricular mechanoreceptors causes an increase in arterial perfusion pressure, which results in greater blood volume and reflex coronary vasodilatation [44, 45]; higher perfusion pressures promote vasoconstriction. However, stimulation of coronary artery baroreceptors also promote reflex vasodilatation [46]. These reflex responses following mechanoreceptor stimulation may confer protection against arterial injury and thereby slow progression of coronary artery disease.

Local release of prostaglandins, nitric oxide (NO) and endothelium-derived relaxation factors stimulate activation of select populations of cardiac neurons that contribute to vasoregulation. NO contributes to neuronal mediated vasoregulation; NO induced vasodilatation involves adrenergic, myogenic and hormonal influences [47, 48]. NO in concert with other vasoactive mediators effectively counteracts vasoconstrictor mechanisms [49–51]; these effects may be gender dependent. Three nitric oxide synthase (NOS) isoforms that synthesize NO from L-arginine have been documented; of these, two are constitutively expressed Ca^{2+}-dependent isoforms—eNOS (endothelial) is localized in cardiocytes as well as vascular and endocardial endothelium while nNOS (neuronal) is found in cardiac neurons [52–54]. The ubiquitous nature of NO implies a role in regulation of central nervous system, myocardium and vascular function [55]; nNOS and cardiac inhibitory G protein are believed to work in parallel in order to reduce sinus node rate and thereby modulate heart rate variability [56]. NO directly affects intrinsic cardiac neurons; almost 40% of these neurons are NOS positive [57]. Altered neuronal effects of NO may be important in pathogenesis of hypertension, septic shock, diabetes mellitus, etc.

Studies from our laboratory, in dogs subject to acute cardiac decentralization, indicated that intrinsic cardiac neurons function independently of central neuronal inputs. In decentralized and innervated hearts coronary autoregulation was similar (**Figure 1**) despite substantial reductions in myocardial oxygen demand (in decentralized hearts) [58]. In addition, perfusion across the ventricular wall (in decentralized hearts; **Figure 2**) was preserved thus confirming
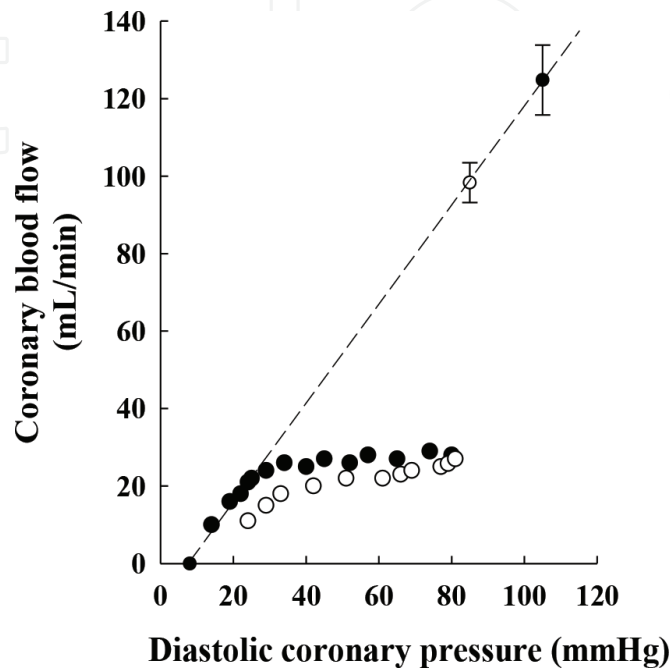

Figure 1. Coronary blood flow versus diastolic coronary artery pressure during autoregulation. Pressure-flow relations in dogs with intact cardiac nerves (closed circles) and after extracardiac nerve ablation (open circles) are shown. Note the similarity between the two curves; reactive hyperemia blood flow was lower in decentralized dogs as shown.
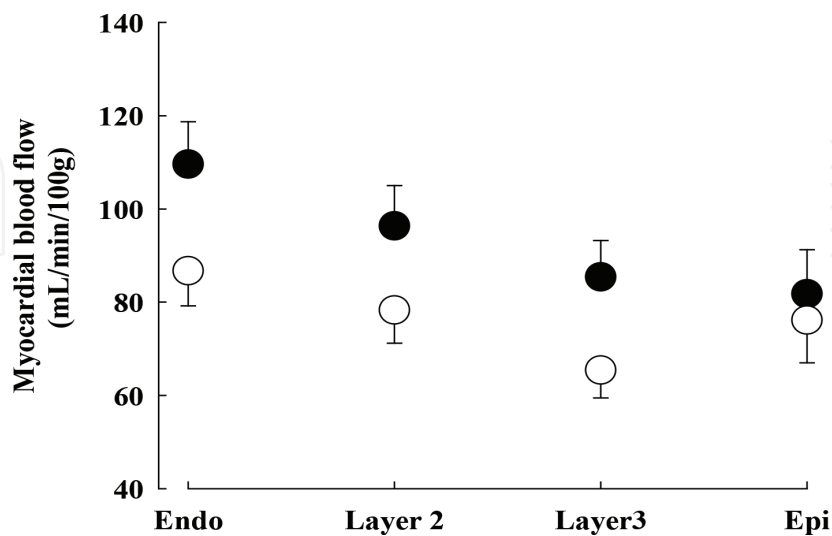

Figure 2. Myocardial blood flow distribution across the ventricular wall (measured with microspheres) in hearts from dogs with intact cardiac nerves (closed symbols) and after acute cardiac decentralization (open symbols). Data are means ± SEM.

earlier findings of Rimoldi and coworkers [59] who reported no change in transmural distribution of myocardial blood flow after regional sympathetic denervation. Stability of perfusion across the ventricular wall was suggested to be due to several factors including neuronal modulation, autoregulation and variations in coronary resistance at the microvessel level (<100 μm). Interestingly, in neuropathy patients the innervation/ventricular perfusion ratio during reactive hyperemia is lower in innervated compared to denervated regions within the ventricular wall [60]. These findings are considerably different from those reported in human subjects after suppression of adenosine-mediated sympathetic activation [61].

4. Ischemic injury

4.1. Nervous system

Ischemia significantly modulates function of intrinsic cardiac neurons because of local accumulations of metabolic by-products (i.e. reactive oxygen species, purinergic compounds, etc.) [62–64]. A limited number of animal studies have investigated the overall effects of ischemia on activity of nerves that course over, or through infarcted myocardium [65]; findings indicate that blood supply to these cardiac nerves is not a determining factor for conduction of action potentials [66]. The question of whether, or not, cardiac nerves are more, or less, sensitive to ischemia is less adequately studied; consequently, the injury threshold of cardiac nerves and neurons remains unknown. However, it is possible that activity of cardiac neurons post-ischemia is preserved consequent to stimulation of ventricular sensory neurites that transduce mechanical and chemical milieu in the myocardium [67]. During acute myocardial ischemia, norepinephrine is released from sympathetic nerves; this triggers sympathetic nerve regeneration (i.e. sprouting, budding) and nerve remodeling to promote sympathetic hyperinnervation, which ultimately plays a role in arrhythmogenesis [68–72]. Function of cardiac sympathetic neurons post-ischemia can also be triggered by the elevated production of intra-neuronal galanin (i.e. promotes regeneration of sympathetic axons) [73]; galanin modifies synaptic transmission and contributes to arrhythmogenesis and sudden cardiac death. Additionally, multiple autacoids (adenosine, bradykinin, NO, reactive oxygen species, etc.) produced during ischemia stimulate the central nervous system, cardiac autonomic ganglia and sympathetic efferent postganglionic axons in coronary vessels [74, 75]. Neuropeptide chemicals released from sensory neurites also modulate intrinsic cardiac neuronal activity [41, 76]. It is interesting to speculate that common survival pathways of cardiac neurons may be shared with cardiocytes but this has not been established.

4.2. Heart

Infarction causes major changes between peripheral and central aspects of the cardiac nervous system; structural and functional alterations at the cardiomyocyte level include; (1) changes in collagen matrix [77], (2) induction of electromechanical dyssynchrony [78], (3) ventricular contractile dysfunction [79], apoptosis [80], etc. In the heart, ischemia affects the ICNS which is the convergence point for cardiac neural control. As such, afferent inputs are modulated

along with descending neural inputs [78] (i.e. including reflex-induced sympathoexcitation and reduced central drive from parasympathetic nerves [81, 82]). Heightened sympathetic tone partly mediated by neurotransmission through the stellate ganglia has been linked to cardiac pathogenesis as well as risk of cardiac arrhythmias and sudden death [83, 84].

Acute coronary artery occlusion produces distinct alterations in cardiomyocyte pathology that ultimately contribute to cell death; for cardiac myocytes a transmural gradient of cell death occurs in relation to duration and degree of ischemia [85, 86]. Transmural necrosis is mostly manifest by 6 h after acute coronary occlusion; the potential for tissue salvage after this time is limited (i.e. species dependent). Physiopathology of ischemic injury is generally well-documented [87–90]; numerous cytoprotective strategies to limit ischemic injury (i.e. pharmacologic, endogenous, etc.) have been tested but none has achieved widespread clinical use [90–92]. Post-ischemic remodeling of sympathetic neurons in stellate ganglia is not well established; however, a potential relation exists between ganglion inflammation and oxidative stress [93]. A recent study in rodents documented greater oxidative stress (i.e. lipofuscin accumulation, mitochondrial degeneration, etc.), metabolic activity (higher rate of lipid peroxidation) and inflammation in stellate glial cells [94]. These physiopathological mechanisms are believed to contribute to local inflammation (i.e. leukocyte infiltration) within stellate ganglia; this stimulates neuronal activity and oxidative stress, which increases cardiac afferent neurotransmission [95]. Other contributing factors include circulating neurohormonal compounds (i.e. angiotensin II, etc.) and brainstem-mediated increases in efferent sympathetic outflow [96–98]. Equally, cardiac inflammation and oxidative stress produced by repeated defibrillation are involved in ganglion pathology [99].

The importance of cardiac nerves for the pathogenesis of post-ischemic infarct development and cardiac dysfunction has been investigated in experimental models of ischemia-reperfusion injury. In cardiac decentralized pigs, significant ventricular dysfunction accompanied by patchy subendocardial necrosis occurs after acute coronary occlusion [100]; myocardial perfusion-function relations in these animals were not affected by nerve status. In addition, we reported coronary vascular reserve to be comparable after nerve ablation albeit in a different experimental model [101], which is consistent with most published findings [102–105]. We also confirmed a trend towards smaller infarcts in dogs subject to extracardiac nerve ablation or pharmacologic decentralization using the autonomic ganglionic blocker hexamethonium bromide (**Figure 3**) [106]; these findings are also in agreement with earlier studies documenting increased tolerance to ischemic injury and a reduction in ventricular fibrillation threshold post-decentralization [102, 107, 108]. Reduced oxygen demand and improved perfusion of affected tissues could be responsible for increased ischemic tolerance of myocytes [43, 104, 105, 109] in the absence of intact cardiac nerves. Of note, extracardiac surgical ablation of sympathetic and parasympathetic efferent neuronal inputs produces a decentralized (not denervated) heart without complete elimination of parasympathetic involvement [110, 111]; on the other hand, pharmacologic ganglionic blockade with hexamethonium bromide blocks transmission within peripheral autonomic ganglia and vagal cardio-acceleration [112]. Continued research into the identification of endogenous compounds that modulate or activate intrinsic neuronal populations to induce cellular protection remains a priority.
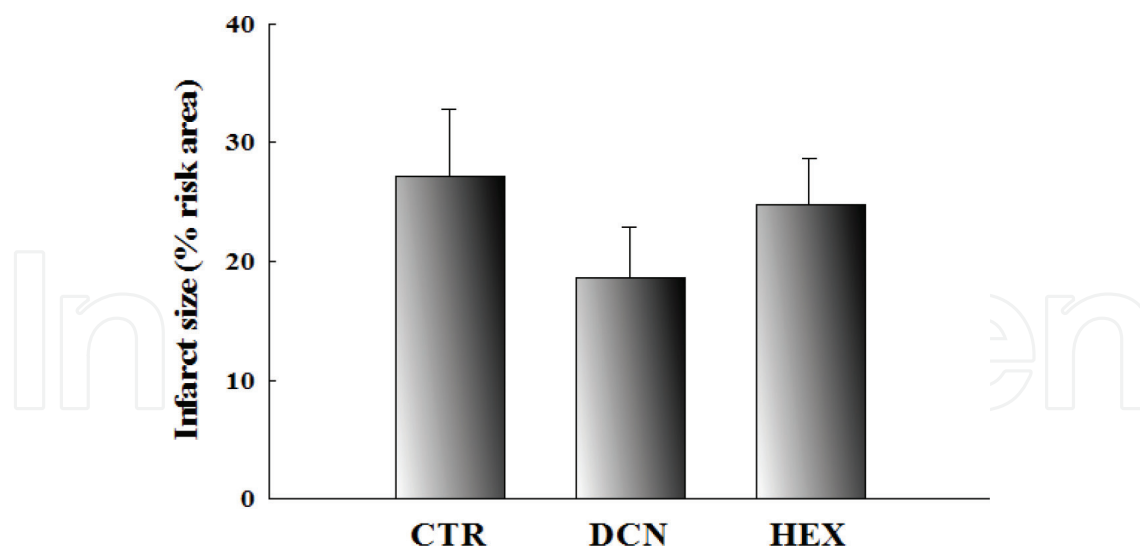
Figure 3. Histogram of myocardial infarct size (as percent of anatomic area at risk) in dogs undergoing ischemia–reperfusion injury. Three distinct groups are shown: (1) control (CTR); (2) acute cardiac decentralized (DCN) and (3) hexamethonium bromide (HEX). Data are mean ± 1SD; n = 8/group.

4.3. Cardiac arrhythmogenesis

Sudden cardiac death due to ventricular arrhythmias is highly relevant to cardiovascular disease related mortality [113]; autonomic neuronal dysfunction is a major contributor to induction of atrial and ventricular dysrhythmias [114–116]. Pathologically induced disturbances in neural processing within the cardiac neural hierarchy affect efferent neuronal outputs throughout the myocardium [19, 117] (i.e. intrinsic and extrinsic cardiac ganglia, central reflexes [95, 118–121]). Cardiac neurons are generally classified as afferent, efferent or convergent on the basis of responses to various cardiovascular stimuli [31, 120]. A study from Ardell's laboratory examined functional remodeling of neuronal elements within the context of myocardial infarction [120]; they showed that: (1) morphological and phenotypic remodeling of intracardiac ganglia is dependent on the site of injury, (2) attenuation of afferent neural signals to intrinsic cardiac neurons (i.e. within ischemic zone) but preservation of these signals in remote and border regions (i.e. neural sensory border zone), (3) autonomic efferent inputs to intrinsic cardiac neurons are maintained, (4) transduction capacity increases in convergent intrinsic local circuit neurons (of the heart) and (5) connectivity of intrinsic cardiac neurons is reduced. Current findings suggest that neuronal remodeling can occur independently of direct injury to specific neuron subsets; as such, neuronal plasticity within the cardiac neuroaxis is crucial post-infarction and during progression of cardiovascular disease [122, 123]. Indeed, healed myocardium provides a particular challenge to electrical propagation and regulation of cardiac function [124, 125]; abnormal cardiac efferent signaling results in continuous discord between central and peripheral aspects within the neural hierarchy that produces fatal arrhythmias due to excessive sympathoexcitation [122]. The peri-infarct region (i.e. interface between dense scar and surviving myocardium) also has an increased potential for ectopic beats [71, 126]. Ajijola and coworkers recently determined that (1) despite scarring, myocyte loss and ion channel remodeling significant regulation of electrical activation

occurs via cardiac sympathetic nerves within the peri-infarct region, and (2) there is significant remodeling of sympathetic innervation within the anteroapical region [127]; additionally, they emphasized the critical role of adrenergic activation in modulating propagation patterns.

Premature ventricular contractions (PVC; contraction of the ventricles caused by abnormal electrical activity) often lead to cardiovascular events, left ventricle dysfunction and sudden cardiac death [128]; multiple mechanisms have been proposed including mechanical dyssynchrony, abnormalities in calcium handling and oxygen consumption and autonomic imbalance [122, 129, 130]. Hamon and coworkers documented (using *in vivo* cardioneural mapping) that PVCs are a powerful stressor for the ICNS and that PVC-induced neural and electrophysiological changes are critical for arrhythmogenesis and remodeling. PVCs with variable coupling intervals have a more complex impact on cardiac neurons than those with fixed short or long coupling intervals [128]. The unpredictability of coupling intervals could trigger a sympathovagal imbalance that influences cardiomyocyte function and leads to electric instability. Greater neuronal responses (particularly within convergent neurons that are responsible for reflex processing) to variable compared to constant stimulus (i.e. neural adaptation) have been described in sensory neurons of the visual, auditory and olfactory systems [131, 132]. In the heart sympathetic nerve activity is greater during irregular cardiac pacing and is independent of hemodynamic changes [133]. As such, increased variability of PVC coupling interval could play a role in reflex activation of the ANS. Greater understanding of underlying mechanoelectric mechanisms of PVC-induced arrhythmogenesis should help to improve risk stratification in cardiac patients that would allow use of more aggressive pharmacologic and non-pharmacologic therapeutics (i.e. specifically targeting the ANS) in prophylactic management (cf. **Table 1**).

	Pertinent studies
Pharmacological interventions	
• Neuregulin-1	[134–138]
• Ghrelin	[139]
• Vasopressin	[140]
• Anesthetic preconditioning	[141]
Non-pharmacological interventions	
• Transcutaneous electrical nerve stimulation (TENS)	[142–144]
• Bioelectronic block	[145–148]
• Spinal cord stimulation (SCS)	[118, 149–152]
• Vagal nerve stimulation (VNS)	[78, 153, 154]
• Renal nerve denervation	[155–157]
• Cardiac decentralization and carotid body ablation	[158–162]
• Cardiac conditioning (ischemia, exercise)	[21, 163, 164]

Table 1. Management strategies that target the autonomic nervous system.

5. Therapeutic interventions

5.1. Pharmacological

Pharmacologic interventions can play an important role in post-ischemic nerve repair; though most medications reduce the incidence of arrhythmias some can be proarrhythmic [165]. Significant improvement in acute and chronic ischemic cardiomyopathy, myocarditis and vagus nerve remodeling have recently been reported in clinical and experimental studies with different pharmacological approaches such as epidermal growth factor neuregulin-1 (NRG1) [134, 138, 166–168]. NRG1 is a key factor for cardiac development [136, 169]; NRG1 activates tyrosine kinase causing a host of cardiovascular effects: (1) regulation of structure and function in cardiomyocytes (i.e. apoptosis, cell proliferation), (2) promotion of angiogenesis and (3) downregulation of sympathetic nerve mRNA and protein expression levels to inhibit nerve remodeling [134, 135, 137, 170].

5.2. Non-pharmacological

Cardiovascular disease is often accompanied by increased activity of carotid body chemoreceptors, which induces an autonomic imbalance [161]; ablation of carotid bodies has been documented to markedly improve post-ischemic cardiovascular end-points in clinical and animal studies [159, 160, 171]. Catheter ablation techniques have been used effectively in patients with ventricular tachyarrhythmias [147]; in addition, bilateral cardiac stellate decentralization (removes excessive sympathetic input to cardiomyocytes) is used in subjects that do not respond to conventional treatments [158]. A drawback of the latter intervention is that it is permanent and generally accompanied by secondary effects [172]. Of note is that the ICNS preserves the ability to coordinate neural activity and electrical stability even after disconnection of inputs from higher central command (i.e. brain) [173].

Specific neuron subpopulations can be targeted for neuromodulation therapy [174–176]; spinal cord stimulation (SCS), vagus nerve stimulation (VNS) and bioelectronic therapy (i.e. charge-balanced direct current, axonal modulation, kilohertz (kHz) frequency alternating current, etc.) are used in ischemic heart disease patients to abate reflex activation of peripheral ganglia [118, 147, 148, 174, 177, 178]. Application of electric current by stimulation/suppression of action potential propagation along nerves modulates neuron and organ function [145, 179]. Blockade of action potential propagation is produced by either kHz frequency alternating current or direct current; these protocols are used repeatedly and safely in patients [145, 147, 180].

SCS stimulates sympathetic afferents to transduce signals, which initiate from the ischemic myocardium, to spinal cord dorsal horn neurons [121, 181]. In the majority of patients receiving this treatment beneficial effects (i.e. improved exercise capacity, quality of life, etc.) last for more than a year [182, 183]. Additionally, SCS augments resistance to stress in myocytes by modifying myocyte energetics [177, 184]; in our laboratory, we documented that concurrent SCS did not influence post-ischemic ventricular perfusion [150].

VNS, on the other hand, protects myocardium [185–187] through anti-adrenergic interactions (i.e. higher parasympathetic activity stimulates muscarinic receptor activation that

limits excess adrenergic receptor activation [188]) within intrinsic cardiac ganglia [189, 190] combined with reduced release of norepinephrine from presynaptic mechanisms in ischemic myocardium [191]. VNS also influences myocyte energetics due to its regulatory effects on glycogen metabolism [78, 185]; all of these factors can change sensory transduction within the cardiac milieu in the event of disparities between oxygen and nutrient supply and demand.

Salavation and co-workers have examined potential differences between SCS and VNS with regard to their ability to alter cardiac sensory neurons in nodose ganglia to transduce the ischemic myocardium; they reported that these interventions differentially obtund nociceptive-related nodose afferent neuronal inputs to the medulla but do not affect mechanosensitive transduction capabilities [192]. These nerve stimulation techniques are presently being tested in a number of clinical trials in heart failure patients (i.e. NECTAR-HF, ANTHEM-HF, INOVATE-HF) with promising results [153, 193, 194].

Intact neural pathways may be unimportant for protection of ischemic myocardium; this is most apparent in the transplanted heart where autonomic ganglia are disconnected from central neurons [121, 195]. Endogenous compounds released into the bloodstream or locally near nerves, neurons and cardiomyocytes, etc. during ischemia could stimulate intracellular pathways that transduce cytoprotective mechanisms. For instance, cardiac conditioning, which significantly delays development of post-ischemic tissue injury [91, 196–198], might involve activation of the ICNS (cf. recent review [90]). A variety of conditioning stratagems (both pharmacologic and non-pharmacologic) that trigger cellular transduction pathways (guanylate cyclase, kinases, etc.) mediate cellular protection through end-effectors; significant cross-tolerance exists with regard to the mechanisms involved [106, 199, 200].

6. Conclusions

Neurocardiology involves dynamic exchange between neurohumoral control systems and the cardiac milieu; bi-directional interactions between sympathetic and parasympathetic efferent pathways regulate inter-organ communications at different levels of the neuraxis. This is evident in the cardiac conditioning paradigm (i.e. pre-, per-, post- and remote) where endogenous ligands and catecholamines trigger intracellular transduction pathways to mediate cytoprotective end-effectors that promote cell survival [201, 202]. Strategies that protect against non-lethal ischemic injury could depend on nervous system status the question of how cytoprotective signals are transmitted between organs remains crucial. New findings support the concept that disorders within the ANS contribute to pathogenesis of organ injury, co-morbidities [203, 204] and even survival. Improved comprehension of modifications within the cardiac-neuro axis at the molecular, cellular, organ and whole body levels are critical for development of therapeutic strategies.

Acknowledgements

Conflict of interest

The authors have no conflicts of interest to declare.

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