

# World Journal of *Cardiology*

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## Influence of cardiac nerve status on cardiovascular regulation and cardioprotection

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### Abstract

Neural elements of the intrinsic cardiac nervous system transduce sensory inputs from the heart, blood vessels and other organs to ensure adequate cardiac function on a beat-to-beat basis. This inter-organ crosstalk is critical for normal function of the heart and other organs; derangements within the nervous system hierarchy contribute to pathogenesis of organ dysfunction. The role of intact cardiac nerves in development of, as well as protection against, ischemic injury is of current interest since it may involve recruitment of intrinsic cardiac ganglia. For instance, ischemic conditioning, a novel protection strategy against organ injury, and in particular remote conditioning, is likely mediated by activation of neural pathways or by endogenous cytoprotective blood-borne substances that stimulate different signalling pathways. This discovery reinforces the concept that inter-organ communication, and maintenance thereof, is key. As such, greater understanding of mechanisms and elucidation of treatment strategies is imperative to improve clinical outcomes particularly in patients with comorbidities. For instance, autonomic imbalance between sympathetic and parasympathetic nervous system regulation can initiate cardiovascular autonomic neuropathy that compromises cardiac stability and function. Neuromodulation therapies that directly target the intrinsic cardiac nervous system or other elements of the nervous system hierarchy are currently being investigated for treatment of different maladies in animal and human studies.

**Key words:** Intrinsic cardiac nervous system; Myocardial ischemia; Ischemic conditioning; Autonomic neuropathy; Coronary blood flow regulation

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**Core tip:** Neural elements within the intrinsic cardiac nervous system are known to transduce sensory inputs from the heart, blood vessels and surrounding organs

to ensure beat-to-beat regulation of cardiac function. Development of autonomic neurophathies in patients with comorbidities compromises clinical outcomes. Myocardial ischemia also significantly affects cardiocytes as well as cardiac neurons; post-ischemic remodeling might affect neuronal function and thereby contribute to cardiac instability. Different protection strategies including ischemic conditioning and neuromodulation interventions that limit neural injury and help maintain cardiovascular function are the subject of ongoing investigations.

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## INTRODUCTION

A dense network of parasympathetic, sympathetic and sensory neurons innervates the heart and cardiac conduction system; each population of neurons is distinct with respect to functional requirements of the heart. Increased attention is being focused on the complex anatomy and function of the cardiac neuroaxis and questions abound regarding the manner in which different neuronal populations communicate with each other and between different organ systems. Ardell *et al.*<sup>[1]</sup> recently made the case that the cardiac neural hierarchy functions as a distributive processor with multiple nested feedback control loops that involve peripheral and central aspects of the autonomic nervous system. Remodeling of the cardiac nervous system at morphological and phenotypic levels during disease development is also under scrutiny<sup>[2-5]</sup>; neural remodeling can cause electrical instability that increases the incidence of arrhythmogenesis. Neuromodulation-based treatments for cardiovascular disease are being investigated as evidenced by the increasing use of diverse cardiac sympathetic decentralization and bioelectric interventions<sup>[6]</sup>. Herein, we briefly discuss experimental and clinical findings that highlight a role for the intrinsic cardiac nervous system on cardiodynamics. We also discuss mechanisms relevant to diverse protection stratagems. Finally, we focus on autonomic neurophathies that accompany comorbidities (Figure 1). For this review, clinical and basic science reports were searched using MEDLINE, PubMed and Google Scholar with the keywords intrinsic cardiac nervous system, myocardial ischemia-reperfusion injury, heart and kidney disease, cardioprotection, preconditioning and combinations thereof. Findings from our own studies on this, and related subjects were also consulted.

### Developmental aspects

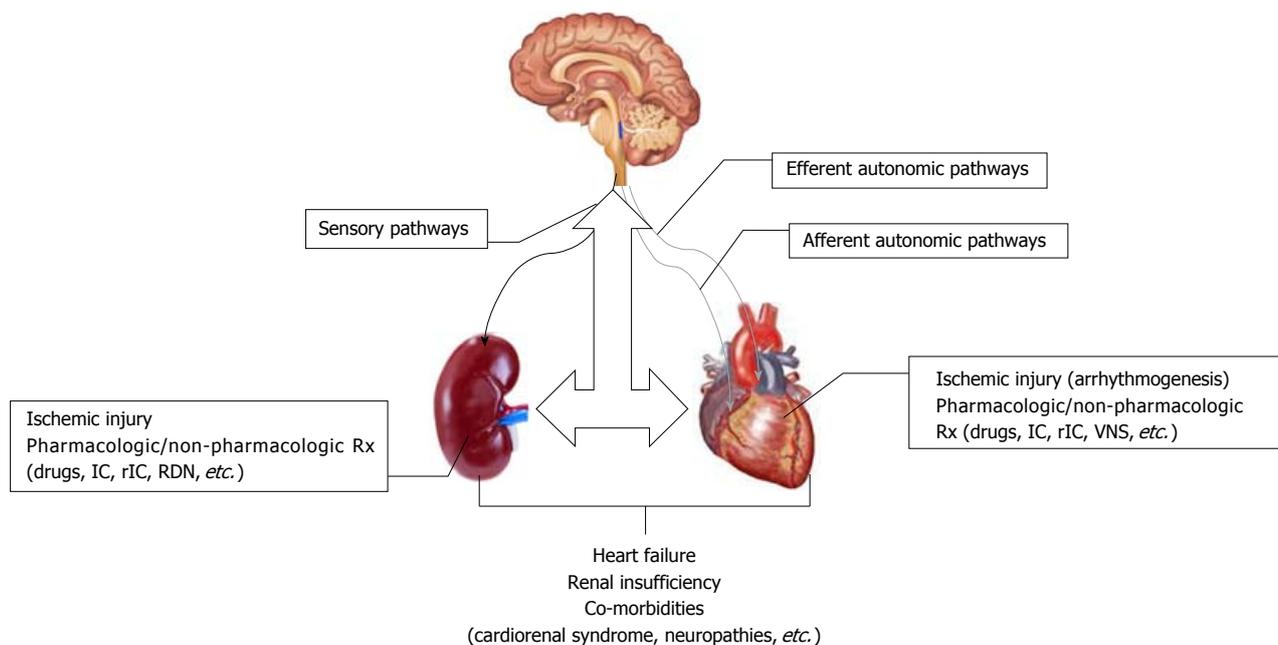
Development of the nervous and cardiovascular systems is synchronized during embryogenesis; neural crest cells in the dorsal neural tube form the parasympathetic and

sympathetic nervous systems that are important for cardiovascular function. Sympathetic interactions play a part in postnatal regulation of cardiocyte maturation; during life, cardiocytes remain quiescent and heart size increases by cellular hypertrophy<sup>[7]</sup>.

Cardiac neural crest cells furnish mesenchymal cells to the heart and great arteries that are involved in vascular remodeling and development of the cardiac conduction system<sup>[8-10]</sup>. The sympathetic component of the autonomic nervous system promotes cardiac conduction while the parasympathetic selectively exerts an inhibitory influence<sup>[11,12]</sup>. The integration of information for neurocardiac regulation involves the neuraxis that comprises the cortex, amygdala and various subcortical structures with an ability to modulate lower-level neurons within the hierarchy (for a detailed explanation see ref.<sup>[12]</sup>). Principal contacts between preganglionic neurons and the heart occur *via* the vagus nerves<sup>[2,13]</sup>. Neurons of the autonomic nervous system are: (1) characterized by chemical phenotyping (cholinergic, adrenergic, *etc.*); (2) located within intrathoracic extracardiac ganglia and intrinsic cardiac ganglia<sup>[14,15]</sup>; and (3) found within atrial epicardium and ganglionated plexi along major vessels and in the ventricular wall<sup>[16,17]</sup> depending on species<sup>[18]</sup>. Sensory neurons, interneurons and sensory fibers that originate from the nucleus ambiguus are also located therein<sup>[19,20]</sup>. Sensory information from all of these peripheral structures is integrated with higher central nervous system centers to coordinate regulation of cardiovascular responses. For example, descending signals from higher brain centers as well as afferent sensory signals from systemic arteries, cardiopulmonary regions and viscera have their first synapse in the nucleus tractus solarius (NTS) found in the dorsomedial region of the medulla<sup>[21]</sup>. Transmission of afferent inputs from other sources such as skin and skeletal muscle to medullary vasomotor centers occur *via* the spinal cord. Vagal outflow to the heart is mediated by NTS neurons that synapse to preganglionic parasympathetic neurons located in the dorsal motor nucleus. All of these neural inputs to medullary vasomotor centers are involved in autonomic control of the cardiovascular system, for example, the arterial baroreceptor reflex plays a major role in blood pressure homeostasis on a beat-to-beat basis and involves stretch receptors that can be found in the carotid sinus and aortic arch. Accordingly, afferent baroreceptor discharge is relayed from the carotid sinus (*via* glossopharyngeal nerve) and aorta (*via* vagus nerve) to the NTS that stimulates afferent baroreceptor discharge and promotes efferent sympathetic and parasympathetic outflow to the heart and blood vessels, this enables adjustments of cardiac output and vessel resistance and ultimately facilitates return of blood pressure to steady state levels.

## CORONARY BLOOD FLOW REGULATION AND MYOCARDIAL PERFUSION

Non-neural mechanisms (humoral, metabolic, mechanical,



**Figure 1** A schematic overview of efferent and afferent autonomic pathways on normal cardiac regulation, they also play a role in arrhythmogenesis caused by ischemic injury. Various pharmacologic/non-pharmacologic interventions that target autonomic pathways (IC: Ischemic conditioning; rIC: Remote IC; VNS: Vagus nerve stimulation) attenuate cardiac or renal symptoms. Sensory pathways are involved in renal regulation; injury (all cause) affects renal function that can be attenuated by different interventions (IC, rIC, RDN: Renal denervation). Inter-organ interactions also directly affect organ function; development of comorbidities is related to pathogenesis of disease in multiple organs (ex. heart-kidneys-brain, etc.). Pathology in one organ system can result in significant progression of disease in a distant organ; neuromodulation interventions may be beneficial to these patients.

etc.) that contribute to control of vascular regulation act independently from autonomic neural mechanisms. For example, under normal physiological conditions myocardial perfusion across the ventricles is uniform as long as coronary artery pressure is maintained within the range of autoregulation<sup>[22]</sup>. Shifts in the lower pressure limit are produced by changes in left ventricular pressure and volume as well as biochemical modifications by a host of endogenous compounds that exercise their effects on myocytes, conduction tissues, vascular smooth muscle, etc. The scientific literature that has examined coronary vasoregulation with a focus on cardiac nerve status is relatively sparse. Most studies have concentrated on control of regional cardiodynamics by the intrinsic cardiac nervous system in either normal or pathological conditions.

In healthy individuals during exercise, activation of the sympathetic nervous system stimulates metabolic vasodilatation due to increases in heart rate, cardiac contractility and ventricular work. Direct sympathetic stimulation of coronary vessels induces either vasoconstriction or vasodilatation depending on activation of either  $\alpha$ -, or  $\beta$ -adrenoreceptors, or vessel size. For example, large coronary vessels (> 100  $\mu\text{m}$ ) constrict when exposed to norepinephrine whereas small coronary vessels relax<sup>[23]</sup>; vasodilatation in arterioles permits coordination of oxygen delivery to myocardial oxygen demand<sup>[24]</sup>. On the other hand, simultaneous vasoconstriction in medium and large coronary arteries mediated by activation of  $\alpha$ -adrenoreceptors helps to preserve subendocardial blood flow when oxygen demand increases. In a canine study,

we examined myocardial perfusion following injection of select neuropeptides into active loci of the intrinsic cardiac nervous system and documented significant coronary vasodilatation secondary to increased myocardial metabolism and oxygen demand<sup>[25]</sup>. We also examined whether intact cardiac nerves were critical for coronary blood flow autoregulation; results confirmed a role for intrinsic cardiac neurons in autoregulatory control and myocardial perfusion even after ablation of extracardiac nerves from central nervous system control<sup>[26]</sup>. Ablation of external neuronal inputs to the heart also results in reduced myocardial efficiency that is consistent with impaired glucose utilization and depletion of cardiac catecholamine levels<sup>[27,28]</sup>; the latter directly affect myocardial oxygen demand<sup>[29-31]</sup>. Other animal studies reported that heterogeneity of myocardial perfusion is similar in innervated and denervated hearts<sup>[32-34]</sup>; possible explanations include: (1) the fact that regional denervation has little effect on vascular  $\alpha$ -adrenergic receptors (in part due to circulating catecholamines); or (2) preserved neural modulation and autoregulation at different levels of the microcirculation across the ventricular wall<sup>[35,36]</sup>.

Diverse central and peripheral elements within the cardiac nervous system act in sync to regulate cardiac function<sup>[20,37]</sup>; direct stimulation of intracardiac neurons occurs through central efferent neuronal inputs from the vagi or stellate ganglia<sup>[38]</sup>. G-protein coupled receptors are known to regulate cardiac function (see recent review by Capote *et al.*<sup>[39]</sup> on structure, function and signalling pathways solicited by G-protein-coupled receptors in the heart). Control of heart rate requires intricate

coordination between  $\beta$ -adrenergic and muscarinic cholinergic receptors found throughout the cardiac conduction system. Cardiac contraction controlled by  $\beta$ -adrenergic receptors are found in myocyte membranes while cardiac structure and morphology are coordinated by angiotensin II type 1 receptors in fibroblast and both endothelial cell and myocyte membranes<sup>[40,41]</sup>. Highly distinct processing capabilities of intracardiac neurons allow this complex network to respond to multiple inputs from all cardiac regions and major vessels near the heart. Disruption of these control networks by diverse cardiac pathologies ultimately increases the potential for sudden cardiac death<sup>[42-45]</sup>.

## MYOCARDIAL ISCHEMIA

Myocardial ischemia significantly influences cardiocytes as well as local and remote neurons that are involved in regulation of cardiac function<sup>[1,46]</sup>; the survival threshold of intra-/extra-cardiac sympathetic/parasympathetic neurons during development of coronary artery disease is not well established. However, viable nerves that course over an infarcted region tend to remain so oxygen and energy needs are fulfilled by an independent blood supply from extracardiac sources<sup>[47]</sup>. Reorganization of cardiocytes and nerves during development of diverse cardiac pathologies could occur in response to shifts of cardiac demand and function<sup>[3,48]</sup>. Mechanisms involved in the pathogenesis of cardiac dysfunction are multifactorial; a short list of possible factors include cardiac substrates, neural/cardiocyte interface, hormonal influences, inflammation and reflex responses between intra- and extra-cardiac nervous systems and their interactions with higher center neurons. Cardiocytes and cardiac neurons conceivably share common pathways for survival but this remains to be proven.

In the setting of transient ischemia, intact cardiac nerves are believed to play a key role on post-ischemic restoration of cardiac function<sup>[49]</sup>. Direct ischemic effects include progressive neuronal dysfunction and regional nerve terminal sprouting which ultimately diminishes local sensory and motor neurite function<sup>[50,51]</sup>. Indirect effects that modulate local neurite function are caused by local release of a host of endogenous chemicals (purinergic agents, peptides, hydroxyl radicals, *etc.*) that also affect neuronal function. Post-ischemic remodeling of cardiac neural networks could promote conflicts between central and peripheral reflexes that increases the risk of autonomic imbalances, arrhythmogenesis and sudden cardiac death<sup>[3,15,37,52]</sup>. A recent position paper by Ardell *et al.*<sup>[1]</sup> discussed the significance of remodeling of the cardiac neuronal hierarchy to cardiac arrhythmia induction. In addition, inotropic stimulation is deleterious to myocyte survival as it occasions an imbalance between oxygen demand and supply (*i.e.*, increased oxygen demand with limited coronary vascular reserve)<sup>[49,53]</sup>.

Acute occlusion of a coronary artery produces distinct alterations of myocyte pathology that lead to cell death unless blood flow is restored to the affected myocardium,

a transmural gradient of cell death occurs in relation to the duration of ischemia and degree of blood perfusion *via* coronary collateral vessels to the underperfused myocardium<sup>[54]</sup>. In animal models, necrosis is generally fully developed by 6 h after which tissue salvage is not possible (this time frame may not be the same for human myocardium) with currently available interventions. In addition, early restoration of blood flow to an infarct-related coronary vessel could cause "reperfusion injury" in already damaged or otherwise affected myocytes<sup>[55]</sup>. The physiopathology of ischemic, or reperfusion injury has been reviewed and discussed over the past several decades<sup>[56-59]</sup>; however, less attention has focused on the ability of the cardiac nervous system to accommodate the stress of ischemic, or reperfusion injury. Post-ischemic changes in peptide expression due to release of inflammatory cytokines combined with nerve damage could affect neuropeptide production in sympathetic cardiac neurons. In one study, Habecker *et al.*<sup>[60]</sup> documented extensive axon damage after infarction; they also reported a significant increase of galanin (promotes regeneration of sensory neurons<sup>[61]</sup>) in cardiac sympathetic neurons in the left ventricle. These findings indicate that cardiac sympathetic neurons retain a certain capability to respond to nerve growth factor which is increased during ischemia-reperfusion<sup>[62]</sup>.

While sympathetic dysinnervation has been reported secondary to myocardial infarction, the injury threshold of sympathetic and parasympathetic cardiac neurons within the ischemic region has not been established<sup>[63,64]</sup>. Several studies have documented that sympathetic impairment could exceed the area of underperfusion and necrosis<sup>[65,66]</sup>. Ischemic stress stimulates release of autocooids such as adenosine and bradykinin, along with nitric oxide and reactive oxygen species that can trigger cellular signal transduction pathways. These compounds can initiate responses in somata and axons within the intrinsic cardiac nervous system<sup>[37]</sup>. Indeed, oxidative stress, changes in growth factor expression and inflammatory cytokines released within the heart and vasculature contribute to neuronal remodelling<sup>[2,3,5,67]</sup>. As mentioned earlier, the regenerative capacity of cardiocytes is limited<sup>[68]</sup>; cardiocytes withdraw from the cell cycle early after birth and subsequently remain quiescent. Transition from proliferative to hypertrophic growth corresponds to the period of sympathetic growth into the heart tissues; *in vitro* studies with neonatal cardiocytes cultivated in the presence of innervating sympathetic fibers showed significant cellular proliferation<sup>[69]</sup> thereby confirming that early sympathetic signalling plays a role. In earlier *in vitro* studies, Horackova *et al.*<sup>[70]</sup> reported that adult ventricular myocytes co-cultured with intrathoracic neurons retained similar structural properties to those observed *in vivo*; cardiocytes and intrinsic cardiac neurons that were cultured alone displayed a variety of morphologies (unipolar, bipolar, multipolar).

Sympathetic regulation might also be involved in myocyte regeneration following ischemia, or reperfusion, injury; however, disruption of peripheral nerves inhibits

regeneration<sup>[71,72]</sup>. Chemical sympathectomy blocks early regeneration of damaged myocytes and increases tissue scarring<sup>[73]</sup>. Though additional studies are necessary, available data support the role of the intact cardiac nervous system on cardiocyte development and proliferation. On the other hand, post-ischemic regeneration and remodeling of the cardiac nervous system also merits further consideration and investigation. Rajendran *et al*<sup>[46]</sup> recently evaluated post-ischemic changes in neural signalling in a porcine model; they presented a “cardiac electroneurogram” between injured and adjacent non-injured myocardial tissue and reported: (1) that different intra-cardiac ganglia undergo morphological and phenotypic remodeling depending on the site of injury; (2) attenuation of afferent neural signals from the infarcted region to intra-cardiac neurons (activity in border and remote regions is apparently preserved); (3) maintenance of autonomic efferent inputs to the intrinsic cardiac nervous system; (4) augmented transduction capacity of convergent intrinsic cardiac local circuit neurons; and (5) reduced network connectivity within the intrinsic cardiac nervous system. The heterogeneity of afferent neural signals probably results from the presence of a “neural sensory border zone” (*i.e.*, analogous to the so-called myocardial border zone) caused by scar formation during post-ischemic myocardial healing. This infarct-induced asymmetry of afferent inputs probably contributes to reflex activation of the autonomic nervous system; recent findings from Wang *et al*<sup>[74]</sup> using resiniferatoxin (a potent agonist of transient receptor potential vanilloid 1) showed reductions in cardiac afferent nociceptive signalling, and sympatho-excitation along with preserved cardiac function in rat hearts.

The role of intact cardiac nerves in modulating responses to ischemia and post-ischemic ventricular function has been studied in a variety of experimental models. In a cardiac decentralized porcine model subject to acute coronary artery stenosis Huang *et al*<sup>[49]</sup> reported significant ventricular dysfunction accompanied by patchy subendocardial necrosis; they proposed that the impaired recovery of left ventricular function is mediated by nitric oxide (NO) and reactive oxygen species (ROS). Cardiac nerves may help to attenuate production of ROS and/or prevent conversion of NO to peroxynitrite (*via* release of still unknown mediators/scavengers); neurotransmitters from cardiac nerves could stimulate or upregulate different isoforms of nitric oxide synthase (*i.e.*, endothelial, neural)<sup>[75]</sup>. Myocardial perfusion-function relations are not altered by cardiac denervation<sup>[49]</sup>; this can be partly explained by the similarity between intact innervated and denervated hearts with regard to determinants of myocardial oxygen demand. In a recent study, we reported no significant change in coronary vascular reserve (intact cardiac nerves *vs* acute decentralized) in a canine model of ischemia-reperfusion injury<sup>[76]</sup>; these findings concur with most<sup>[77,78]</sup>, but not all, earlier studies<sup>[79]</sup>. Of particular note is that protection against ischemic injury occurred even when affected myocardium was disconnected from central command;

this suggests that local intrinsic cardiac neurons share common protection pathways to delay progression of cellular necrosis. Neurotransmitters that originate from cardiac nerves or intrinsic cardiac neurons might stimulate release of endogenous compounds that activate intracellular signalling pathways involved in cytoprotection; they could also inhibit peroxynitrite formation by modulating activation of various nitric oxide synthase isoforms. Indeed, many questions remain regarding the role of intact cardiac nerves within the context of cardioprotection against ischemia-reperfusion injury.

Myocardial ischemia also results in excessive activation of extracardiac cholinergic and adrenergic inputs of local circuit neurons within the intrinsic cardiac nervous system<sup>[38,80]</sup> that initiate cardiac arrhythmias<sup>[81]</sup>. A novel treatment for suppression of ventricular arrhythmias and treatment of refractory angina pectoris in current use in preclinical and clinical studies is spinal cord stimulation<sup>[80,82-84]</sup>; this intervention alters peripheral ganglia neural processing along the neural end-organ interface<sup>[85,86]</sup> and transduces neural signals to higher centers *via* the spinal cord<sup>[1,87,88]</sup>. Spinal cord stimulation influences autonomic reflexes within the neuroaxis and stimulates discharge of neuromodulators that limit release of select neurotransmitters and alter basal activity of sympathetic preganglionic neurons<sup>[89,90]</sup>. Intermittent spinal cord stimulation is suggested to stimulate neural memory and may be used for management of cardiac control and angina<sup>[91]</sup>; this could be akin to “electrical conditioning” and may be useful to limit cellular injury caused by ischemia. Vagus nerve stimulation is also being used to protect against ischemic injury and its consequences<sup>[92]</sup>; vagus nerve stimulation activates a host of signalling pathways and inhibits release of pro-inflammatory cytokines (see Ardell *et al*<sup>[1]</sup> for an up-to-date review). Vagus nerve stimulation might also affect myocardial energetics and maintain the equilibrium between energy supply and demand in the failing heart<sup>[93,94]</sup>. Interventions using vagus nerve stimulation favourably modulate cardiac disease as well as arrhythmogenesis; in several clinical studies this non-pharmacologic treatment is safe and well tolerated and is documented to improve cardiodynamics in patients with compromised ventricular function<sup>[95,96]</sup>.

## MYOCARDIAL PROTECTION

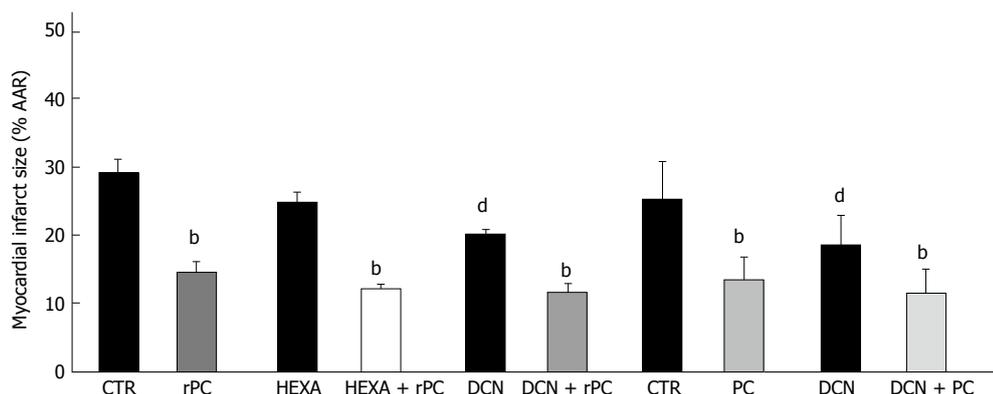
Sympathetic and parasympathetic nerves located near cardiocytes permit rapid crosstalk between cell types that may, or may not, activate cytoprotective pathways. Ischemic conditioning was first described by Murry *et al*<sup>[97]</sup> in 1986 in barbiturate-anesthetized dogs subjected to repeated episodes of sublethal coronary occlusion/reperfusion in advance of a prolonged period of acute ischemia. To date, ischemic conditioning has been reported to delay development of cellular necrosis in all organs examined in animals and in humans<sup>[98]</sup>; two distinct windows of cellular protection have been described but the causative mechanism(s) remain unanswered. The reader is referred to a recent review that summarizes

research into this cytoprotective intervention over the past 30 years<sup>[99]</sup>. Interestingly, Kudej *et al.*<sup>[100]</sup> showed that intact cardiac nerves were not required for first window protection in a porcine ischemia-reperfusion injury model; however, the presence of functional cardiac nerves was considered essential for development of second window protection. This delayed protection could occur through  $\alpha_1$ -adrenergic receptor pathways mediated by iNOS and COX-2<sup>[101]</sup>.

A host of conditioning strategies have been described in animal and clinical studies; however, the potential to translate conditioning-mediated protection in patients remains controversial<sup>[102,103]</sup>. Remote conditioning was first described in dogs subject to acute coronary occlusion and was referred to as "preconditioning at a distance"<sup>[104]</sup>. In that study, animals were subject to repetitive periods of non-lethal ischemia of the left circumflex artery vascular bed before exposure to a prolonged occlusion of the left anterior descending coronary artery; results demonstrated that a cytoprotective factor could be activated, produced, or transported from the heart or elsewhere to affected tissues to afford protection. Since the publication of these key findings numerous studies using remote conditioning either before, during or after coronary occlusion have been reported<sup>[105-109]</sup> but the mechanisms involved have not been established. An important but unanswered question that persists is how the protective signals are transferred from distant tissues to the target organ. Various hypotheses (not mutually exclusive) including: (1) communication *via* blood or perfusate borne humoral factors; (2) communication by neuronal stimulation and transmission; and (3) communication by systemic alteration of circulating immune cells have been proposed<sup>[106,110,111]</sup>. Intrinsic neural loops in the heart process sensory information from the myocardium that modulate efferent autonomic output from the intrinsic cardiac ganglia even in the absence of input from the central nervous system<sup>[37,38,93,112]</sup>. Transmission of sensory messages within intrinsic cardiac ganglia is regulated by release of acetylcholine into the synaptic cleft; nerve impulses are initiated by acetylcholine that activates specific receptors in post-ganglionic nerves<sup>[112-114]</sup>. The risk of injury or remodeling of these neural loops escalates during myocardial ischemia; studies with pharmacologic ganglionic blockade document abolition of remote conditioning-mediated cytoprotection and suggest that protective signals could transfer between organs *via* neural pathways<sup>[112,115-117]</sup>. Early preclinical studies in different experimental models (including heart failure) reported positive results with vagal nerve stimulation (VNS) with respect to ventricular remodeling, ejection fraction and biomarker levels<sup>[118-120]</sup>. In patients with advanced heart failure, VNS reportedly attenuates left ventricular contractile dysfunction<sup>[121]</sup> and may reduce ischemic injury<sup>[122-124]</sup>. Clinical studies show that diminished heart-rate responses and depressed sensitivity of vagal reflexes are associated with poor cardiovascular outcomes and cardiac-related mortality<sup>[125-127]</sup>. Smith *et al.*<sup>[127]</sup> recently reviewed efficacy of VNS for hypertension and heart failure in several small,

randomized clinical trials (ANTHEM-HF, NECTAR-HF, INOVATE-HF, *etc.*) and concluded that further studies are required; VNS titration studies are also needed to validate potential clinical benefits of these interventions<sup>[128]</sup>. Stimulation of vagal nerves activate a host of signalling pathways *via* increased release of acetylcholine that activates downstream receptors (cholinergic, muscarinic, *etc.*) to impact cardiodynamics and could also promote myocyte resistance to stress by improving myocyte energetics<sup>[93]</sup>. Cross-talk between humoral mediators and neural pathways could also produce cytoprotection by stimulation of local afferent nerves<sup>[129,130]</sup>; but it remains unclear whether intact, functional nerves are required to assure conditioning-mediated cytoprotection<sup>[131,132]</sup>. On the basis of data showing that intact sensory innervation of peripheral ischemic tissue is essential to remote conditioning protection, Mastitskaya *et al.*<sup>[133]</sup> proposed a "remote preconditioning reflex" that requires sensory input from remote ischemic tissue; recruitment of vagal pre-ganglionic neurons within the dorsal motor nucleus of the vagus nerve was considered to be critical for cytoprotection. While this data does not negate the concept that humoral factors are required for protection by remote conditioning, they strongly suggest that functional neurons within the parasympathetic nervous system are critical<sup>[134,135]</sup>. Bilateral vagotomy reportedly abolished protection afforded by remote conditioning<sup>[136]</sup>. On the other hand, findings from our laboratory (summarized in Figure 2) documented significant protection against ischemic injury independent of intact extrinsic cardiac nerves (note the similarity between groups with respect to reduction in infarct size) regardless of the conditioning protocol<sup>[76,137]</sup>. Briefly, in those studies isoflurane anesthetized dogs underwent remote conditioning (4 × 5-min renal artery occlusion/reperfusion) combined with/without treatment with the autonomic ganglionic blocker, hexamethonium (HEXA; 20 mg/kg, *IV*) or acute cardiac decentralization (DCN). Additional experiments were performed in dogs subject to classical preconditioning either before or after DCN. Based on these findings we suggested that neural pathways might not directly influence ischemic conditioning (either classical or remote) mediated cardioprotection. Moreover, others have brought forward the view that intact connections between the heart and central nervous system are not necessary for remote conditioning-mediated cardioprotection as long as recruitable parasympathetic neurons within a target organ can be activated. Use of remote conditioning as a potential therapeutic intervention for organ protection in man continues to merit investigation because it is non-invasive, cost-effective and easily applicable; however, the period for successful application of this intervention has yet to be determined and clinical strategies aimed at reducing myocardial damage by ischemic conditioning have been unsuccessful. While cellular protection by ischemic conditioning is possible in the presence of comorbidities, a stronger triggering stimulus appears necessary to assure cytoprotection<sup>[138]</sup>.

Understanding bidirectional interactions between



**Figure 2** Myocardial infarct size (% anatomic area at risk: AAR) is shown for different study groups subject to ischemia-reperfusion injury. Data are means  $\pm$  1SD; <sup>b</sup> $P \leq 0.01$  vs respective control (CTR), HEXA (hexmethonium; 20 mg/kg, IV), or DCN (acute cardiac decentralized) group; <sup>d</sup> $P \leq 0.01$  vs CTR groups. Group differences determined by ANOVA. PC: Ischemic preconditioning; rPC: Remote preconditioning. Data reported in earlier studies from our laboratory<sup>[76,137]</sup>.

elements of the nervous system and its remodeling during evolution of different comorbidities (senescence, kidney dysfunction, diabetes, *etc.*) is essential to help in the development of strategies to delay progression of disease not only in the heart but also in other organs. For instance, autonomic neuropathies defined by abnormalities of the sympathetic and parasympathetic nervous systems could be responsible for significant morbidity and mortality in patients; cardiovascular events are considered a primary risk factor for mortality. Cardiovascular autonomic dysfunction is the result of complex interplay between vascular, neural, cardiac, paracrine and endocrine entities; the outcome is tissue injury that compromises integrity of cardiac reflexes.

## HEART FAILURE

Heart failure subsequent to cardiac injury or chronic stress causes significant loss of contractile efficacy. Investigations into the role of autonomic imbalance between sympathetic and parasympathetic nervous systems and its contribution to pathogenesis of heart failure is ongoing for more than 25 years. Altered autonomic function also plays a role in other cardiac interrelated conditions such as hypertension, myocardial ischemia, cardiac arrhythmogenesis and sudden cardiac death<sup>[48]</sup>, see recent review by Florea and Cohn<sup>[139]</sup>. Dynamic interactions between cardiocytes and compensatory neurohumoral mechanisms allow the heart to maintain cardiac output; stimulation of the adrenergic nervous and renin-angiotensin-aldosterone systems along with activation of cytokines play a critical role to prevent progressive worsening of cardiac function associated with heart failure<sup>[140,141]</sup>. Lympopoulos *et al.*<sup>[141]</sup> recently reviewed: (1) the actions of neurotransmitters on cell surface adrenergic and G-protein-coupled receptors; and (2) adrenergic receptor polymorphisms in the physiopathology of heart failure. They concluded that activation of the autonomic nervous system plays a critical role in compensatory responses to progressive cardiac dysfunction; however, excessive activation of these compensatory pathways could accelerate development

of heart failure. In addition, they examined various therapeutic approaches (*i.e.*, sympathomimetic drugs, activation of cardiac parasympathetic nervous system, increasing  $\beta$ -adrenergic receptor function using novel G-protein-coupled receptor blockade, *etc.*).

## CHRONIC KIDNEY DISEASE AND NEUROPATHY

Physiopathology of chronic kidney disease (CKD) is complex and results either from a primary renal disorder or from multisystem disorders related to various comorbidities such as diabetes. Indeed, diabetes is considered to be the most common cause of CKD in patients. Neurological derangements are a common occurrence in CKD<sup>[142]</sup>. The spectrum of CKD ranges from mild kidney damage (largely asymptomatic) to end-stage renal disease (potentially fatal); neurological complications that include cognitive dysfunction, stroke, as well as peripheral and autonomic neuropathy can markedly affect clinical outcomes<sup>[143]</sup>. Accumulation of urea, creatinine, parathyroid hormone in high concentrations provide a biochemical milieu that rapidly produces neurological dysfunction; however, most symptoms can be reversed with treatments such as hemodialysis<sup>[144]</sup>. Mechanisms responsible for increased cardiovascular risk in patients with CKD are multifactorial and include hypertension and diabetes<sup>[145]</sup>, along with increased oxidative stress, decreased bioavailability of nitric oxide, inflammation, abnormal calcium and phosphorous metabolism, overstimulation of the sympathetic nervous system, *etc.*<sup>[146-148]</sup>. Anemia is another major complication associated with both CKD and diabetes<sup>[149]</sup>; the latter may be present before overt evidence of symptoms of renal impairment<sup>[150]</sup>.

Essential structures of the kidneys (renal vessels, tubules, juxtaglomerular apparatus, *etc.*) are richly innervated. Renal afferent nerves transmit sensory information *via* chemo- and mechano-receptors to higher centers within the brain<sup>[151,152]</sup>, to maintain water retention, sodium reabsorption and blood flow. These

nerves might also play a role in renal inflammation and injury; suggested mechanisms include  $\beta$ -adrenergic receptor activation, release of neuropeptides (neuropeptide Y, vasoactive intestinal polypeptide, substance P, *etc.*), renin release from juxtaglomerular cells (increases plasma angiotensin II levels) and other pro-inflammatory cytokines (tumor necrosis factor, IL-1 $\beta$ , *etc.*).

Autonomic dysfunction is prevalent (> 60%) in CKD patients and is associated with vascular calcification, cardiac arrhythmias and sudden cardiac death<sup>[153]</sup>. Reduced sensitivity to baroreceptors in the vessel wall caused by autonomic dysfunction can modulate cardiac regulation and contribute to intradialytic hypotension (*i.e.*, no increase in heart rate to compensate the decrease in arterial pressure)<sup>[154]</sup>; these symptoms can be corrected with pharmaceuticals or, if necessary, renal transplantation.

## DIABETIC AUTONOMIC NEUROPATHY

Autonomic dysfunction is a recognized complication of diabetes mellitus; diverse contributory mechanisms to increased mortality includes medial hyperplasia at baroreceptor sites, impaired cardiac vagal function, left ventricular hypertrophy and endothelial dysfunction<sup>[155]</sup> due in part to oxidative stress and reduced availability of nitric oxide which can affect sympathetic nerve activity<sup>[156]</sup>. Endothelial nitric oxide synthesis is known to be defective in insulin resistant states and is a central factor to neuronal abnormalities during metabolic syndrome (increases cardiovascular risk to some extent due to sympathetic activation)<sup>[155]</sup>. Insulin also plays a key role in nitric oxide and autonomic nervous system interactions and is involved in regulation of peripheral vascular tone and arterial blood pressure. Significant evidence shows that nitric oxide is critical to the vasodilator actions of insulin<sup>[157]</sup>; sympathectomy and autonomic failure can severely limit insulin-induced vasodilatation in patients<sup>[158]</sup>. Vulnerability to lethal arrhythmias in diabetic patients with autonomic dysfunction is also elevated<sup>[159]</sup>. Cardiac autonomic dysfunction may occur more frequently when diabetes is coupled with micro albuminuria caused by microvascular damage and endothelial dysfunction<sup>[160-162]</sup>; however, it was reported in the Hoom Study that cardiovascular autonomic dysfunction and microalbuminuria were independently associated with mortality<sup>[163]</sup>. Additionally, in that study the presence of cardiovascular autonomic dysfunction doubled the 9-year mortality risk<sup>[155,164]</sup>; the ACCORD study also confirmed a significantly higher rate of mortality in patients with autonomic dysfunction<sup>[165]</sup>.

## CONCLUSION

Impaired sympathetic and parasympathetic nervous system regulation contributes to organ dysfunction and leads to significant morbidity and mortality particularly in patients with comorbidities. Early detection and management of these patients could markedly reduce adverse effects and thereby affect clinical outcomes. Prospectively, autonomic dysfunction develops because of

damage at multiple sites within organs but pathogenesis remains to be clarified. Cardiovascular autonomic dysfunction, for instance, reflects compromised interactions between vascular, neural, cardiac, inflammatory, paracrine and endocrine mechanisms. Restoration of autonomic equilibrium in animal and clinical studies using either pharmacologic or non-pharmacologic interventions is currently possible. Further investigations in neurocardiology should continue to provide important findings apropos connections between cardiac and neurohumoral control systems and thereby allow continued development of clinically relevant opportunities for neuroscience-based treatments.

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