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REVIEW ARTICLE

Autonomic control of ventricular function in health and disease: current state of the art

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Abstract

Purpose Cardiac autonomic dysfunction is one of the main pillars of cardiovascular pathophysiology. The purpose of this review is to provide an overview of the current state of the art on the pathological remodeling that occurs within the autonomic nervous system with cardiac injury and available neuromodulatory therapies for autonomic dysfunction in heart failure.

Methods Data from peer-reviewed publications on autonomic function in health and after cardiac injury are reviewed. The role of and evidence behind various neuromodulatory therapies both in preclinical investigation and in-use in clinical practice are summarized.

Results A harmonic interplay between the heart and the autonomic nervous system exists at multiple levels of the neuraxis. This interplay becomes disrupted in the setting of cardiovascular disease, resulting in pathological changes at multiple levels, from subcellular cardiac signaling of neurotransmitters to extra-cardiac, extra-thoracic remodeling. The subsequent detrimental cycle of sympathovagal imbalance, characterized by sympathoexcitation and parasympathetic withdrawal, predisposes to ventricular arrhythmias, progression of heart failure, and cardiac mortality. Knowledge on the etiology and pathophysiology of this condition has increased exponentially over the past few decades, resulting in a number of different neuromodulatory approaches. However, significant knowledge gaps in both sympathetic and parasympathetic interactions and causal factors that mediate progressive sympathoexcitation and parasympathetic dysfunction remain.

Conclusions Although our understanding of autonomic imbalance in cardiovascular diseases has significantly increased, specific, pivotal mediators of this imbalance and the recognition and implementation of available autonomic parameters and neuromodulatory therapies are still lagging.

Keywords Autonomic · Sympathetic · Parasympathetic · Heart failure · Ventricular arrhythmias

Introduction

The autonomic nerves that innervate the heart—in a healthy condition—fine-tune every heartbeat, altering cardiac output to meet the underlying physiological demands of the organism. The beat-to-beat feedback is initiated by afferent nerves traveling from the heart to central and peripheral autonomic integration centers. Upon integration, efferent signals are generated in these relay centers and transmitted to the heart via the cardiomotor neurons of the sympathetic and/or parasympathetic nervous system [1]. As a result, almost all facets of cardiac function (e.g., chronotropy, dromotropy, inotropy, and lusitropy) are continuously regulated. This multitiered arrangement plays a pivotal role in homeostatic cardiac control under healthy circumstances, but is disrupted in cardiovascular diseases, establishing a cycle in which cardiac deterioration and autonomic dysfunction are reciprocally perpetuated.

Afferent innervation

Cardiac autonomic modulation relies on mechano- and chemosensory information transmitted by cardiac afferent neurons. The sensory neurites of these neurons travel with the vagal and sympathetic nerves and relay information to

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(1) the cardiac ganglionated plexi and possibly the stellate ganglia and (2) via the dorsal root ganglia and vagal ganglia to the central nervous system (Fig. 1) [1]. The majority of cardiac sensory neurons seem to have the capability to transmit both mechanical and chemosensory information, though some neurons are selective for one or the other [2, 3]. Transmission occurs via different neurotransmitters, including gamma-aminobutyric acid (GABA) and glutamate. GABA, through depolarizing second-order neurons, inhibits sensory transmission, whereas glutamate is the primary excitatory neurotransmitter of cardiac afferent neurons [4–7].

A set of cardiac afferent fibers travel to the central nervous system via the vagus nerve. The cell bodies of these pseudounipolar neurons, which are also named "vagal afferents," lie in the left and right inferior vagal (nodose) ganglia [1]. In the medulla, these afferents synapse upon second-order neurons in the nucleus tractus solitarius (NTS), some of which activate vagal efferent outflow via synapses onto the vagal nuclei in the brain stem [2, 8]. No laterality in the territory sensed by vagal afferents has been reported [9].

Conversely, another subset of centrally projecting afferent neurons have their somata in the cervical (C6) to high thoracic (T6) dorsal root ganglia. These pseudounipolar neurons synapse onto second-order neurons in the dorsal horn of the spinal cord, and ultimately communicate with higher brain nuclei via the spinothalamic tract (Fig. 1) [10]. Activation of these "spinal afferents" and subsequent integration of the chemo- and/or mechanosensory information in the thalamus, parabrachial gray, and other brain stem and hypothalamic centers results in a predominantly sympathetic

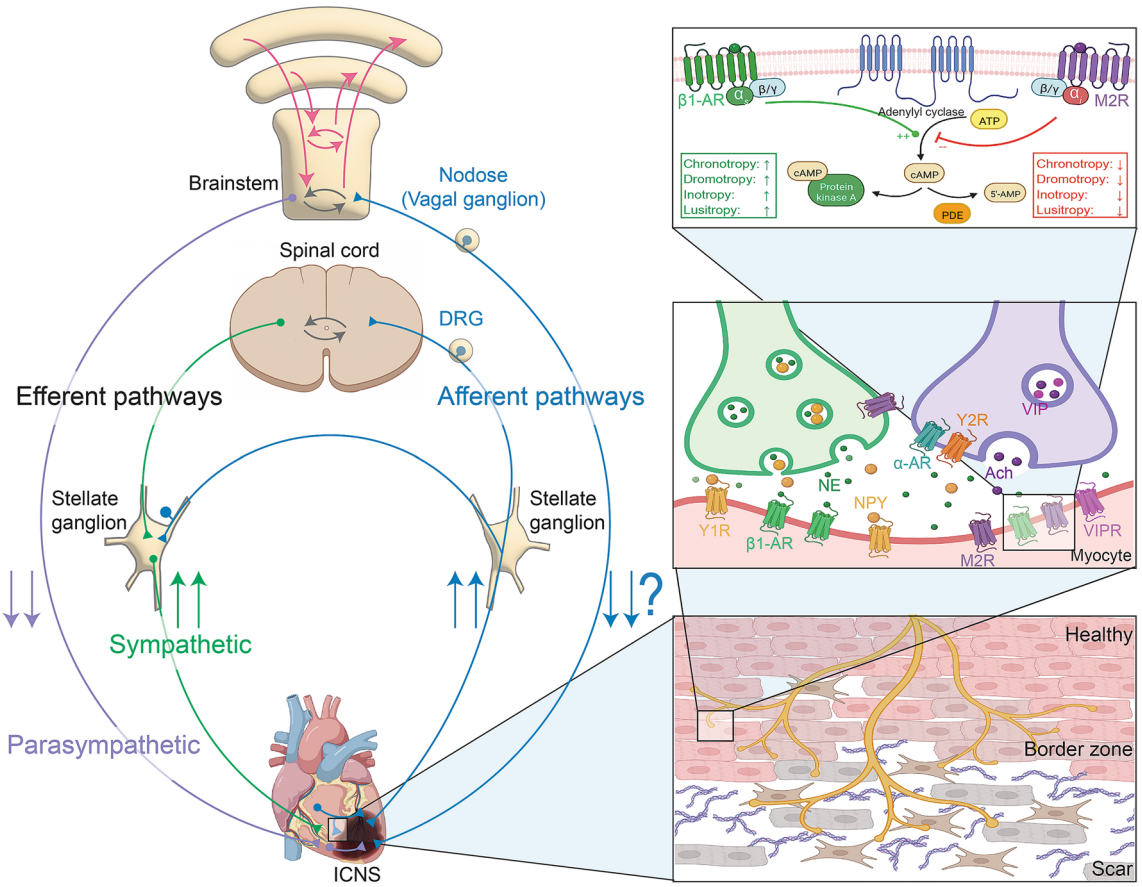

Fig. 1 Cardiac autonomic innervation. Autonomic innervation of the heart is regulated through multiple intrathoracic and extrathoracic reflex loops that consist of afferent (sensory) and efferent (motor) neurons and nerves. Sympathetic afferent activation increases sympathetic outflow to the heart, and vagal afferent activation increases cardiac vagal tone. Cardiac injury, such as a myocardial infarction, increases sympathetic afferent activation, further enhancing sympathoexcitation. Novel data on vagal afferents suggest that remodeling in the vagal ganglia results in reduced neurotransmission, hence decreasing vagal outflow. Myocardial infarction also causes cardiac denervation followed by localized nerve sprouting in the scar and border zone regions. At the level of the nerve–myocyte interface, sympathetic and parasympathetic neurons release different neurotransmitters that establish opposing effects on the heart and inhibit each other's downstream actions. With sympathoexcitation, acetylcholine (ACh) release appears to be inhibited, and specific remodeling of channels and downstream signaling occurs, further enhancing the effects of sympathetic activation on calcium (Ca^{2+}) and cyclic adenosine monophosphate (cAMP) signaling

motor response. This is also known as the cardiac sympathetic afferent response (CSAR) [11, 12].

Other cardiac afferent nerves appear to synapse onto neurons of the intrathoracic ganglia, including the intrinsic cardiac nervous system, and possibly those of the stellate ganglia and thoracic chain, evoking local reflex loops to modulate cardiac function (Fig. 1) [2, 13].

Lastly, cardiac function is also modulated based on sensory information transmitted by extracardiac afferent nerves. Mechanoreceptors in the aortic arch and carotid arteries sense blood pressure and transmit this information to the brain stem. This in turn induces reflexive changes in autonomic efferent tone to preserve cardiac output [8, 14, 15]. Chemosensory neurites in these same peripheral vessels as well as central chemoreceptors in the ventral medulla and retrotrapezoid nucleus sense and transmit information on hypoxemia and hypercapnia, respectively. The integration of these stimuli affects autonomic efferent outflow to properly match ventilation with perfusion [16–18].

Cardiac efferent neurons

Sympathetic and parasympathetic motor neurons modulate cardiac function, often in a "yin-yang" manner [13]. Myelinated preganglionic neurons release acetylcholine (ACh), which binds to nicotinic receptors of postganglionic neurons, depolarizing these neurons, which innervate the myocardium.

Sympathetic efferents

Sympathetic preganglionic neurons receive central input from the rostral ventromedial and ventrolateral medulla, the A5 area of the pons, and the paraventricular nucleus of the hypothalamus (Fig. 1) [1, 13]. Preganglionic sympathetic neurons, which house their cell bodies in the intermediolateral cell column of the spinal cord, synapse onto postganglionic neurons in the left and right sympathetic chain. Cardiac sympathetic postganglionic nerves travel from the stellate ganglia (a fusion of the inferior cervical ganglion and the first thoracic ganglion), T2 to T4, middle cervical, and to a lesser extent, the superior ganglia, to the heart. In addition to central efferent outflow, cardiac afferents synapsing in the stellate ganglia can provoke local intrathoracic extracardiac reflex loops (Fig. 1) [1, 19].

Adrenergic signaling

At cardiac sympathetic nerve varicosities, norepinephrine (NE) is the primary neurotransmitter. Briefly, NE binds to beta-adrenergic receptors, stimulating adenylyl cyclase to increase production of cyclic adenosine monophosphate (cAMP), a key second messenger in the cardiomyocyte signaling cascade. cAMP can activate protein kinase A (PKA) to phosphorylate many downstream targets involved in intracellular Ca^{2+} handling, including phospholamban (PLB), ryanodine receptors (RyR), and L-type Ca^{2+} channels. This leads to an increase in the amount of intracellular Ca^{2+} available for contraction, and therefore, enhances inotropy [20–23]. cAMP also directly activates the funny current (I_f) in pacemaker cells, which accelerates diastolic depolarization, leading to positive chronotropy [24]. The same PKA-mediated changes to intracellular Ca^{2+} handling that contribute to positive inotropy also lead to increased diastolic Ca^{2+} leak from the sarcoplasmic reticulum (SR), which activates the Na^+–Ca^{2+} exchanger (NCX) to remove the excess Ca^{2+}, leading to a net depolarizing current (NCX exchanges 3 Na^+ ions for 1 Ca^{2+} ion). This mechanism, termed the "Ca^{2+} clock," further contributes to diastolic depolarization and positive chronotropy upon beta-adrenergic activation [25–27]. Positive lusitropy (faster relaxation) is aided by PKA phosphorylation of PLB, which relieves inhibition of the SR Ca^{2+}-ATPase (SERCA) pump to increase the rate of Ca^{2+} reuptake into the SR, increasing the rate of relaxation [28]. PKA phosphorylation of troponin I decreases the myofilament's affinity for Ca^{2+}, which also allows for faster Ca^{2+} dissociation and positive lusitropy [29]. Beta-adrenergic activity leads to a PKA-mediated increase in the slow delayed rectifier K^+ (I_{Ks}) current [30]. This repolarizing current opposes increases in depolarizing I_{CaL}, resulting in shortening of the cardiac action potential, and contributes to sympathetic-mediated changes in repolarization (Fig. 1) [31].

In addition to NE-mediated beta-adrenergic effects, sympathetic responses are enhanced by the release of sympathetic co-transmitters, such as neuropeptide Y (NPY) and galanin (Fig. 1). NPY is believed to be released during higher levels of sympathetic activation, and binds Y1-receptors on the myocardium [32, 33]. Y1-receptor stimulation has been shown to impact SR Ca^{2+} handling (in a cAMP-independent manner) and further increases the amount of Ca^{2+} available for contraction [34]. In this way, NPY augments the sympathoexcitatory effects of NE, as sympathetic stimulation is capable of inducing cardiac electrophysiological effects and positive inotropy in the presence of complete beta-blockade [35]. In addition, binding of NPY to Y2-receptors on parasympathetic nerve terminals appears to inhibit cardiac parasympathetic acetylcholine release [36], which could further augment the relative effects of the sympathetic nervous system. Galanin is also co-released by sympathetic nerves, although at lower levels than NPY [33]. Galanin's effects appear to be similar to NPY, as it can also inhibit acetylcholine release by binding to galanin receptors (GalR1) on parasympathetic neurons [33].

Interestingly, even though the postganglionic sympathetic nerves from both the right and the left stellate ganglia release the same neurotransmitters, different cardiac effects are observed by left versus right stellate ganglion stimulation [37, 38]. In part, this difference is due to variability in the areas of innervation; although both sides innervate all aspects of the ventricular myocardium, sympathetic nerves from the right sympathetic chain have more robust innervation of the atria, including the sinoatrial node and the AV-node [39, 40], whereas sympathetic nerves coming from the left sympathetic chain may have more pronounced effects on ventricular contraction [41], though interspecies differences may exist. Furthermore, while stellate ganglia innervate the left ventricular anterior wall, they induce differing electrophysiological effects; left stellate ganglion stimulation enhances electrophysiological heterogeneities to a greater extent than right stellate ganglion stimulation [42], an effect that may be driven by greater heart rate effects of right stellate stimulation, somewhat limiting the extent of regional variability in action potential durations.

Parasympathetic efferents

Parasympathetic preganglionic neurons have their cell bodies in the dorsal motor nucleus and nucleus ambiguus of the medulla (Fig. 1) [1, 13]. These neurons transmit signals via the vagus nerve and synapse onto postganglionic neurons in the cardiac ganglionated plexus, which is part of the intrinsic cardiac nervous system [43]. Thus, in contrast to the sympathetic nervous system, the postganglionic nerves of the parasympathetic nervous system are found near the end organ, and most of the distance is traversed by the myelinated preganglionic fibers (Fig. 1).

Muscarinic signaling

The postganglionic parasympathetic nerves release ACh, which binds to muscarinic (M2) ACh receptors on cardiomyocytes of the atria, sinoatrial and atrioventricular node, and to a lesser extent, ventricles. In contrast to sympathetic innervation, no laterality in cervical vagal cardiac innervation has been reported [44–46]. This observation may be related to the fact that experimentally induced stimulation of preganglionic neurons may allow the postganglionic neurons and close connections within the intrinsic cardiac nervous system (ICNS) to establish a more global and homogeneous response [46].

Binding of ACh to M2 receptors on cardiomyocytes inhibits adenylyl cyclase production of cAMP, thereby opposing the effects of sympathetic-mediated beta-adrenergic receptor stimulation. These opposing effects typically cause negative inotropy, chronotropy, dromotropy, and lusitropy (Fig. 1). ACh (via M2 receptor binding) also increases the ACh-sensitive K^+ current (I_{KACh}), which hyperpolarizes the membrane potential of pacemaker cells, thereby slowing diastolic depolarization and decreasing heart rate [47, 48]. Moreover, the interactions between the sympathetic and parasympathetic nervous system are beyond simply antagonizing myocardial effects. At the level of the nerve terminals, presynaptic receptors modulate sympathetic and parasympathetic neurotransmitter release (Fig. 1) [49]; ACh, released from the parasympathetic nerve terminals, binds to muscarinic receptors on postganglionic sympathetic nerve terminals and inhibits the release of NE [50]. Similarly, activation of alpha-1 receptors and NPY-2 receptors on parasympathetic nerve terminals by NE and NPY has been suggested to decrease release of ACh, though these effects have only been studied in vitro [36, 49, 51].

Finally, the postganglionic parasympathetic nerves also release vasoactive intestinal peptide (VIP), which is released at higher levels of vagal nerve stimulation (Fig. 1). VIP binds to VIP receptors on cardiomyocytes (VPAC1 and VPAC2). These G-protein-coupled receptors stimulate adenylyl cyclase to produce cAMP and have been shown to cause tachycardia via mechanisms similar to those of beta-adrenergic activation [52–54]. VIP may also act at the parasympathetic preganglionic–postganglionic synapses. For example, there is evidence that VIP receptor inhibition enhances the bradycardic response to vagal nerve stimulation, but that VIP receptor inhibition has no effect on resulting bradycardia if postganglionic parasympathetic fibers are activated with nicotine, suggesting a role for VIP in parasympathetic preganglionic–postganglionic signaling [55].

Autonomic remodeling after myocardial infarction and in heart failure with reduced ejection fraction

Cardiovascular disease, such as a myocardial injury, myocardial infarction, or long-standing volume or pressure overload resulting in heart failure, induce autonomic remodeling and progressive sympathovagal imbalance. This process is initially prompted by decreased cardiac output, which increases sympathetic outflow for hemodynamic compensation. Paradoxically, long-standing sympathoexcitation and subsequent autonomic and cardiac remodeling induce pathological myocardial changes that result in a cycle of autonomic dysfunction and cardiac deterioration.

Afferent remodeling

Diminished cardiac function is continuously sensed by cardiac afferents, initiating changes that affect not only afferent neurotransmission but also (central) efferent control.

Vagal afferent remodeling in the nodose (vagal) ganglia was studied by Salavatian et al. [9] in a porcine model of chronic myocardial infarction. An increase in the number of nociceptive, but not mechanosensitive, afferents neurons was observed [9]. Paradoxically, the functional output of these afferent neurons was decreased, and this was associated with an increased expression of the inhibitory neurotransmitter GABA and a decrease in neuronal nitric oxide synthase (nNOS), an afferent neuromodulator with homeostatic properties [56]. In addition, glial fibrillary acidic protein (GFAP) expression by satellite glial cells, a marker of glial activation, was increased [9]. Collectively, these results indicated extensive structural and functional remodeling of vagal afferent neurons after myocardial infarction that resulted in decreased vagal nociceptive afferent neurotransmission.

Spinal afferents, on the other hand, become tonically activated in the setting of cardiovascular disease, resulting in an enhanced CSAR [57], and continuous stimulation of the sympathoexcitatory efferent reflex. This is reflected by increased expression of angiotensin 1 receptors in the nucleus of the solitary tract (NTS), paraventricular nucleus (PVN), and rostral ventrolateral medulla (RVLM), and altered availability of signaling molecules, including reduced nitric oxide [58, 59]. In the dorsal root ganglia, the number of afferent neurons thought to be involved in nociception [characterized by the expression of calcitonin gene-related peptide (CGRP)] was increased after myocardial infarction, and the size of these neurons was also increased [60].

Accordingly, experimental studies have also demonstrated that ablation of transient receptor potential vanilloid 1 (TRPV1)-expressing cardiac nociceptive afferents through the injection of the neurotoxin, resiniferatoxin, in the pericardial space (which ablates both vagal and spinal cardiac afferents) decreased susceptibility for ventricular arrhythmias and improved cardiac function [61, 62].

Lastly, afferent nerve activity in the ICNS is also altered in cardiovascular diseases. This local remodeling includes upregulation of VIP in the ICNS, which might enhance local nociceptive signaling [63].

Sympathetic efferent remodeling

Increased sympathetic efferent outflow is the main outcome of autonomic remodeling in cardiovascular disease, though it may result from multiple pathological adaptations at the level of the central nervous system, the sympathetic chain, and the heart.

As mentioned above, increased spinal afferent signaling promotes central efferent sympathetic outflow to the heart [12, 57]. In the stellate ganglia, postganglionic sympathetic neurons hypertrophy and demonstrate increased synaptic density [64, 65]. Functionally, neurons increase their firing rates and amplitude, while also expressing less nNOS [66–68]. As nNOS normally inhibits NE release from the sympathetic nerves [68, 69] and dampens cardiac effects by inhibition of the L-type Ca^{2+} channels [70], sympathetic activity as well as cardiac effects of sympathetic stimulation become compounded. Interestingly, another hallmark of stellate ganglia remodeling is cholinergic transdifferentiation [71, 72]. Though the exact mechanisms behind this process remains unclear, it is possible that this transdifferentiation may enhance sympathetic outflow through mimicking pre- to postganglionic nerve transmission due to collateral projections from neighboring stellate ganglia neurons [73], as it has now been demonstrated that stellate neurons can activate their neighboring neurons through release of ACh [74]. Moreover, satellite glial cells, which envelope the sympathetic neurons and can modulate their function and activity, also show signs of hyperactivity as indicated by increased expression of GFAP [64].

At the cardiac sympathetic nerve terminals, neural remodeling induces various molecular changes, including a decreased expression of the NE transporter [75] and a paradoxical decrease in NE and tyrosine hydroxylase (TH), the rate-limiting enzyme in NE production [76]. Nevertheless, the increased NE and NPY release due to increased firing rates combined with reduced NE reuptake result in incomplete binding of these neurotransmitters and neuropeptides by their respective cardiac receptors, culminating in their spillover into systemic circulation. Correspondingly, higher plasma levels of NE and NPY have been reported in patients with cardiovascular diseases [77–79]. Increased NE levels may be related to both increased neuronal release of NE and relatively decreased NE reuptake [80]. Increased NE and NPY levels are associated with a poorer survival and increased ventricular arrhythmias after acute myocardial infarction and in heart failure [81–83].

At the level of the heart, autonomic remodeling also alters the distribution and function of sympathetic nerve terminals and their corresponding adrenergic receptors; regions of sympathetic hyperinnervation coexist with patches of sympathetic denervation. For example, nerve growth factor (NGF) becomes acutely upregulated after myocardial infarction and in cardiac hypertrophy, as it tries to promote nerve regeneration (Fig. 1) [84, 85]. However, after chronic myocardial injury, NGF becomes downregulated by continuously increased levels of NE [86, 87]. Even in the setting of elevated NGF, however, many regions of the injured myocardium remain denervated following myocardial infarction, due to the presence of chondroitin sulfate proteoglycans (CSPGs), which can inhibit sympathetic axonal outgrowth [88, 89]. This spatial and temporal variation in neuronal regeneration further enhances heterogeneity in myocardial innervation, predisposing to ventricular arrhythmias [84, 85].

Chronic sympathetic hyperactivity in heart failure results in an overall decrease in beta-1-adrenergic receptor density by approximately 50%, changing the beta-1 to beta-2 receptor ratio (Table 1) [90]. Furthermore, beta-2 receptors, which are normally located within the t-tubules of cardiomyocytes, redistribute to the plasma membrane, resulting in a loss of the normally compartmentalized downstream cAMP signaling [91]. This redistribution may explain the arrhythmogenic consequences of beta-2 stimulation in heart failure [92]. In addition, there is upregulation of the G-protein-coupled receptor kinase 2 (GRK2) [90, 93], which desensitizes the beta-adrenergic receptors on the myocyte and impairs the ability of the heart to respond to sympathoexcitation [94, 95], causing a form of functional denervation, which can exacerbate electrical heterogeneities in response to sympathetic activation. Recently, another kinase in the GRK family, GRK5, has been found to be responsible for switching of the beta-1 signaling from physiological cAMP-PKA to pathological calmodulin-dependent kinase II (CaMKII) activity that contributes to the progression of heart failure [96]. Increased levels of NPY can also cause a downregulation of cardiac NPY-1 receptors in heart failure patients [97], though a paradoxical increase in NPY-2 receptors has been reported in a rat model of heart failure (Table 1) [98]. The functional effects of this upregulation remain to be elucidated. Lastly, density of alpha-1-receptors remains unchanged in the setting of heart failure (Table 1). These receptors seem to exert an important cardioprotective role [99, 100], and blockade of these receptors increases cardiac morbidity and mortality [101, 102]. Heart-failure-induced changes in cardiac receptors and neurotransmitters, coupled with previously described remodeling of ion channels and currents, [103, 104] (Table 1) collectively destabilize cardiac electrophysiology and increase susceptibility to both atrial and ventricular arrhythmias.

Table 1 Changes in expression of cardiac ion currents, channels, and receptors in heart failure

	Up/downregulation
Ion currents and channels	
I_{CaL}	↓ in severe heart failure, ↑ in moderate heart failure
I_{CaT}	↑
I_{f}	↓ in SA node, ↑ in ventricle
I_{K1}	↓
$I_{K,ATP}$	↑
I_{Kr}	↓
I_{Na}	↓
$I_{Na\text{-}K}$	↓
I_{NCX}	↑
I_{to}	↓↓
CAMKII	↑
Cx43	↓
Phospholamban	↓
SERCA	↓
Receptors	
β1-receptor	↓
β2-receptor	=
α1-receptor	↑
NPY-1 receptor	↓
NPY-2 receptor	(↑, rat model)
RYR2	↓

↑: upregulated, ↓: downregulated, =: expression unchanged

Despite the well-known pathological effects of chronic sympathetic hyperactivity in heart failure, loss of sympathetic nerves following myocardial infarction (MI) can also alter signaling and arrhythmia susceptibility. In this respect, the degree of sympathetic nerve loss post-myocardial infarction is an important predictor of arrhythmias and sudden cardiac death [105–107]. Sympathetic denervation can result in areas of beta-adrenergic supersensitivity, observed in patients and large animal models after MI [108, 109]. Denervation is also associated with a downregulation of the transient outward K^+ current (I_{to}) [110], which is responsible for the early phase of repolarization. Therefore, in pathological conditions wherein sympathetic hyperactivity occurs along with regional denervation, the combined effects of elevated catecholamines and regional adrenergic supersensitivity may be particularly arrhythmogenic. Indeed, beta-adrenergic supersensitivity has been experimentally shown to be an important contributor to arrhythmias in the setting of sympathetic hypoinnervation and myocardial infarction [89, 111].

Parasympathetic efferent remodeling

The central and peripheral remodeling processes that underlie parasympathetic withdrawal in the setting of heart failure have been studied to a much lesser extent than sympathetic alterations.

With regard to central parasympathetic function, it was shown that central vagal drive, as reflected by inputs to postganglionic parasympathetic neurons, is reduced after myocardial infarction. Basal activity of neurons in the intrinsic cardiac ganglia that respond to vagal nerve stimulation was decreased, while those that decrease their firing rates with vagus nerve stimulation showed higher baseline activity [112], suggesting reduced central vagal inputs to these neurons. Novel data suggests that vagal afferent neurotransmission is reduced after myocardial infarction, as a result of remodeling that occurs in the vagal (nodose) sensory neurons, reducing efferent vagal tone [9, 113].

In addition, postganglionic neurons in the ICNS express less choline acetyltransferase, whereas muscarinic receptors and VIP expression are upregulated [63, 114, 115]. ICNS

neurons of patients with cardiovascular disease demonstrate hypertrophy, while also exhibiting cytoplasmic inclusions and lipofuscins, markers of degeneration. Nevertheless, myocardial ACh levels and the ICNS neuronal patterns and machinery appear to remain intact. When vagal output is increased with electrical vagal nerve stimulation, myocardial responses remain and are even enhanced in animals after chronic myocardial infarction compared with animals with normal hearts [112].

Lastly, sympathovagal imbalance is further promoted by the antagonizing effects of sympathetic activation on parasympathetic function. As mentioned, release of NPY at the sympathetic nerve terminals has been demonstrated to impede parasympathetic release of ACh in vitro [36]. Moreover, increased spinal afferent signaling might similarly affect parasympathetic withdrawal and dysfunction. However, the precise mechanisms through which sympathovagal imbalance is perpetuated after cardiovascular injury and how these processes could be targeted clinically require additional (in vivo) investigations.

Autonomic imbalance in other ventricular pathologies

While this review is focused on ventricular autonomic control, it is important to note that the autonomic nervous system plays a role in a vast array of other cardiovascular pathologies, including postural orthostatic tachycardia syndrome (POTS), syncope, atrial fibrillation, baroreflex failure, and more recently, long coronavirus (COVID-19). Moreover, ventricular autonomic instability can also be iatrogenic, for example, ablation of epicardial ganglionated plexi as a treatment for atrial fibrillation paradoxically increased susceptibility for ventricular arrhythmias in large animal models and patients that have previously suffered from a myocardial infarction [116–118]. Finally, given its global impact, much of the research and data on ventricular autonomic control has focused on changes that occur in heart failure and sudden cardiac death related to myocardial injury/infarction. However, the role of the autonomic nervous system in several pathologies that can affect the ventricles, including hypertension, amyloidosis, Takotsubo cardiomyopathy, and autonomically mediated ventricular arrhythmias in specific channelopathies, deserve special mention.

Essential hypertension

Essential hypertension, also known as idiopathic hypertension, affects up to 45% of the adult population worldwide [119]. Neurohumoral dysregulation and consequent sympathetic activation appears to be central to the etiology of hypertension [120–123], and hypertensive animal models and patients exhibit increased plasma norepinephrine spillover compared with normotensive controls [124, 125]. Moreover, autonomic imbalance appears to develop prior to the onset of overt hypertension [126], as reflected by reduced heart rate variability (HRV) with an increased in low-frequency (LF) power and increased NE plasma levels in adults with new-onset hypertension [127].

Sympathetic dysfunction in hypertension has been associated with altered brain stem control of sympathetic outflow from the central nervous system to the periphery [128, 129], as well as increased sympathetic activation via the stellate ganglia [130, 131] and the kidneys [132–134]. Increased renal sympathetic nerve activity results in renal vasoconstriction, thereby decreasing glomerular filtration rate, increasing renal reabsorption of sodium and water, and increasing renal release of renin and norepinephrine, thus promoting increases in arterial pressure and further augmenting sympathoexcitation [132].

In the spontaneously hypertensive rat (SHR), stellate ganglion neurons exhibit greater depolarization-induced calcium transients compared with wild-type control animals [131, 135], which could lead to greater release of NE. At the level of the heart, reductions in presynaptic alpha-2 receptors on sympathetic nerves alleviate presynaptic negative feedback, resulting in greater release of NE from these nerve terminals [136]. Lastly a reduction in NE reuptake by the presynaptic NE transporters in the SHR model has been observed (similar to heart failure), further increasing the amount of NE that is available to bind to postsynaptic receptors [137] and further increasing cardiac sympathoexcitation [131].

Chronic uncontrolled hypertension eventually results in left ventricular hypertrophy in both animal models and patients, which predisposes to heart failure [138, 139]. The chronic state of sympathoexcitation can also lead to desensitization of adenylyl cyclase, resulting in contractile dysfunction and further exacerbation of heart failure [138]. Desensitization of adenylyl cyclase could result from downregulation of beta-adrenergic receptors and/or an increase in Gi protein α-subunits; the latter has been observed in hypertrophied human myocardium from hypertensive patients [140].

Although calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), and aldosterone receptor blockers (ARBs) have been demonstrated to be more effective pharmacological therapies in reducing blood pressure [141], beta-blocker therapy has been shown to reduce renin and angiotensin II levels [142], highlighting a beneficial adjuvant role for beta-blockers in pharmacological treatment of hypertension.

Cardiac amyloidosis

Cardiac amyloidosis is a progressive disease that results in a restrictive cardiomyopathy and heart failure. The continuous extracellular deposition of either amyloid light chains (AL) or amyloid transthyretin (ATTR) can result from different etiologies, including genetic mutations, multiple myeloma, or age [143]. Regardless of the etiology, cardiac interstitial infiltration results in ventricular wall thickening, stiffness, and diastolic dysfunction [144]. In addition, amyloid deposits in nerves, leading to neuronal death throughout the body, including in the sympathetic ganglia and vagus nerve [145, 146]. Consequently, cardiac autonomic balance becomes disrupted due to cardiac denervation of both sympathetic and parasympathetic fibers, resulting in depressed heart rate variability and impaired baroreflex sensitivity [147, 148]. Clinically, Holter monitoring, HRV, and heart rate turbulence (HRT) have demonstrated that the degree of autonomic dysfunction in these patients negatively correlates with survival [149–151]. Treatment of cardiac amyloidosis relies on treating the underlying cause (e.g., chemotherapy in case of multiple myeloma, and/or pharmacological treatment with transthyretin stabilizers). Currently, tafamidis is the only Food and Drug Administration-approved transthyretin stabilizer for AATR cardiac amyloidosis [152]. Compared with placebo, treatment with tafamidis has been associated with reductions in all-cause mortality, cardiovascular-related hospitalizations, and reduced decline in quality of life [153]. However, the effects of tafamidis on cardiac autonomic remodeling are yet to be determined. Novel therapies that might become implemented in clinical practice in the near future include transthyretin gene silencing agents and anti-transthyretin antibodies [154]. The efficacy of these drugs on restoring cardiac autonomic balance has yet to be established.

Patients suffering from cardiac amyloidosis should also receive pharmacological treatment for heart failure symptoms. Notably, beta-blockers and inhibitors of the renin–angiotensin–aldosterone system, though standard of care for other etiologies of heart failure, are generally poorly tolerated in this setting, and calcium channel blockers are contraindicated [148]. Moreover, even though the incidence of sudden cardiac death in patients with cardiac amyloidosis is high, internal cardiac defibrillators have failed to show a benefit in this patient population [148, 155, 156].

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is an acute cardiac syndrome, most frequently seen in postmenopausal women [157]. Its clinical presentation is similar to that of an acute myocardial infarction, often presenting with chest pain, ST-segment deviations on the surface electrogram, and elevated plasma troponins [158, 159]. However, rather than coronary artery disease, acute heart failure resulting from left ventricular apical and/or mid-ventricular wall motion abnormalities underlie this acute presentation [158, 159]. Central to the pathophysiology of Takotsubo cardiomyopathy are elevated catecholamines [160, 161], triggered by either emotional (primary Takotsubo cardiomyopathy) or physical illness/trauma (secondary Takotsubo cardiomyopathy) [158, 159, 162]. These elevated catecholamine levels, subsequently, induce myocardial stunning, resulting in the characteristic apical ballooning during systole that is observed by echocardiography [159].

Several processes are likely to underlie this pathophysiology, including catecholamine induced microvascular dysfunction and coronary artery spasm [163, 164], as well as direct cardiac effects of catecholamines on ventricular myocytes [165, 166], inducing calcium overload, mitochondrial dysfunction, and reactive oxygen species production, among other effects. Moreover, using an induced pluripotent stem-cell cardiomyocyte model, the myocytes from Takotsubo cardiomyopathy patients were found to have increased sensitivity to beta-1 receptor stimulation compared with healthy age-matched controls [167]. Correspondingly, Vaccaro et al. [168] observed an increase in spontaneous sympathetic nerve activity (as measured via microneurography) and decreased spontaneous baroreflex control in patients suffering from with Takotsubo cardiomyopathy. Finally, HRV measurements are significantly depressed (i.e., representative of greater sympathetic tone) in patients with acute Takotsubo syndrome [169, 170].

In approximately 95% of Takotsubo cardiomyopathy patients, left ventricular ejection fraction makes a full recovery within several weeks. However, a few studies have suggested that long-term mortality and morbidity rates may be similar to patients that suffer from an acute myocardial infarction [171, 172]. Correspondingly, Norcliffe-Kaufmann et al. [173] found that patients who had a history of Takotsubo cardiomyopathy had exaggerated sympathetic and decreased parasympathetic responses during baroreflex testing (Valsalva maneuver and tilt testing, respectively) [173]. This data suggests that, even after functional hemodynamic recovery of Takotsubo cardiomyopathy, autonomic dysfunction persists.

There are no randomized clinical trials that have evaluated optimal medical therapies in patients suffering from either acute or long-term Takotsubo cardiomyopathy. The major objective for treatment of Takotsubo cardiomyopathy in the acute phase appears to be hemodynamic support, in which mechanical support can be considered in patients with progressive circulatory failure and cardiogenic shock [174]. In patients with a left ventricular ejection fraction of $< 40\%$, ACEI, ARBs, and beta-blockers should be administered, though in case of left ventricular outflow tract obstruction,

inotropes should not be used [174]. There appears to be no clear consensus on the usage of these drugs long-term. Whereas some studies suggest that ACEI and ARBs reduce the risk of Takotsubo cardiomyopathy recurrence (while beta-blockers do not), other studies suggest that none of these therapies reduce the risk of recurrence [175–177]. Additional studies are, therefore, needed to better understand the role of these medications in the chronic treatment of Takotsubo cardiomyopathy.

Long QT syndrome

Various congenital mutations have been identified to result in long QT syndromes (LQTS), generally characterized by prolonged repolarization duration and increased susceptibility to sudden cardiac death [178–180]. LQTS1, LQTS2, and LQTS3, with their respective mutations in *KCNQ1*, *HERG* and *SCN5A,* account for the large majority of LQTS cases [181].

Sympathoexcitation, induced by physiological or physical stress, is a notorious cause of ventricular arrhythmias in patients with LQTS1 and LQTS2 [182]. Whereas sustained sympathetic activation promotes ventricular arrhythmias in LQTS1, ventricular arrhythmias in LQTS2 are induced by a sudden increase in sympathetic tone [183, 184]. In contrast to LQTS1 and LQTS2, ventricular arrhythmias in LQTS3 occur in the setting of decreased sympathetic activity (e.g., during sleep) [184].

In a background of prolonged repolarization, an increase in sympathetic tone predisposes to early afterdepolarizations, whilst also increasing repolarization heterogeneity and, thereby, reinforcing the arrhythmogenic substrate [182]. In LQTS1, sympathetically induced increases in depolarization current are insufficiently counterbalanced by repolarization currents, resulting in a paradoxical increase in action potential duration [184]. This effect is clinically replicated through exercise or epinephrine infusion, both resulting in a prolonged QT interval as well as increased spatial dispersion of repolarization (reflected in greater T-peak to T-end intervals) [185–189]. In LQTS2 repolarization is similarly hampered during sympathoexcitation. However, the subsequent prolongation of repolarization is only transient, as intact IK_s counterbalances the increased depolarization currents [184]. Similar to LQTS1, sympathetic stimulation will also increase spatial dispersion of repolarization, but this effect is also temporary [184]. Clinically, exercise testing and epinephrine infusion corroborate this transient effect of sympathetic activation in LQTS2 [185, 188, 190, 191].

In addition to the increased susceptibility to arrhythmias in the setting of sympathoexcitation, Rizzo et al. [192] observed inflammatory changes in the stellate ganglia of LQTS patients (including LQTS1 and LQTS2), who required cardiac sympathetic denervation for control of refractory ventricular arrhythmias. It is possible that this T-cell mediated neurotoxicity in the stellate ganglia disrupts cardiac sympathetic innervation and tone, which can further augment electrical instabilities during sympathetic stimulation. Correspondingly, metaiodobenzylguanidine (MIBG) studies on LQTS patients show an overall decrease in sympathetic nerve terminals, combined with heterogeneous patterns of cardiac sympathetic innervation, which could further augment the arrhythmogenic substrate [193, 194].

Due to the clear role of the sympathetic nervous system in ventricular arrhythmogenesis in LQTS1 and LQTS2, sympathetic blockade with beta-blocker therapy (i.e., nadolol or propranolol) remains the cornerstone of treatment in these patients [195–200]. However, in patients in which beta-blockers are contraindicated or who suffer from a high arrhythmia burden despite optimal pharmacological treatment, left cardiac sympathetic denervation (CSD) has been proven to be an effective anti-arrhythmic treatment [180, 199, 201–205].

Catecholaminergic polymorphic ventricular arrhythmia

Catecholaminergic polymorphic ventricular arrhythmia (CPVT) is inherited arrhythmia syndrome that results most commonly from mutations in *RYR2* or *CASQ2* genes [206–209], causing cellular calcium mishandling. The consequent calcium overload in the sarcoplasmic reticulum and spontaneous calcium release predispose to delayed afterdepolarizations, which can trigger arrhythmias [210–212]. Hence, in a background of sympathoexcitation (e.g., during episodes of physical or physiological stress), calcium handling becomes further disturbed, increasing the susceptibility for both the arrhythmic triggers and the arrhythmic substrate [213, 214]. Moreover, similar to the aforementioned phenotype of chronic ganglionitis in LQTS patients, similar T-cell infiltration has been observed in the stellate ganglia of CPVT patients [192]. Beta-blockers (preferably nadolol) are the first line of therapy for CPVT treatment, possibly in combination with flecainide [215, 216]. The anti-arrhythmic mechanism of flecainide has been studied in CPVT mouse models and shown to inhibit RYR2-mediated calcium release and/or reduce sodium channel availability, thereby increasing the threshold for triggered activity [217, 218]. Similarly, CPVT patients experienced less exercise-induced ventricular arrhythmias while using flecainide, and combined beta-blocker and flecainide therapy were proven to be superior to treatment with beta-blockers alone [216, 219]. In patients in whom pharmacological treatment is not tolerated or insufficiently suppresses arrhythmia episodes, left CSD is a recommended therapeutic option [213, 220, 221].

Clinical parameters of autonomic dysfunction and evidence for neuromodulatory therapies for ventricular arrhythmias and heart failure

Despite the rapid increase in our understanding of cardiac autonomic function in health and disease, much of these potential prognostic parameters are yet to be used consistently at the bedside, and many neuromodulatory therapies have yet to reach patients. Therefore, the remainder of this review will focus on parameters and treatment modalities that are available for clinical implementation.

Clinical parameters of autonomic (dys)function

Plasma levels of norepinephrine and neuropeptide Y

An accessible method for assessing autonomic dysfunction and sympathoexcitation is measurement of plasma NE and NPY levels. Greater NE levels are associated with increased cardiac symptoms and mortality in heart failure and after myocardial infarction, though not LV dysfunction [78, 79, 222]. It is important to note that plasma NE levels reflect not only NE released by the sympathetic nerve terminals but also renal NE spillover.

Similarly, elevated NPY levels are associated with increased severity and mortality in [223] as well as greater susceptibility to ventricular arrhythmias following myocardial infarction [81, 82]. Though easily accessible and relatively noninvasive, a major drawback of NE and NPY level measurement is that they can be influenced by acute and relatively minor changes in autonomic tone.

Heart rate variability

Heart rate variability (HRV) is a noninvasive measure of cardiac autonomic tone that quantifies the beat-to-beat changes in RR intervals, thereby reflecting the relative sympathetic and parasympathetic tone at the level of the sinus node [224]. It can be measured from recordings spanning from minutes to 24 h, though physiological interpretations of the results vary with different recording lengths [225].

Currently, 24-h recordings are often regarded as the "gold standard," since they were demonstrated to have better predictive power than short-term recordings [226, 227].

HRV can be measured in the time or frequency domain. Temporal indices quantify the extent of beat-to-beat RR interval variability. Of the various measures, the standard deviation of consecutive RR interval [excluding premature ventricular contractions (PVCs); the standard deviation of NN intervals (SDNN)] is most often measured (Fig. 2). Lower SDNN corresponds with increased cardiac morbidity and mortality in heart failure patients [228, 229], and is currently considered the "gold standard" HRV parameter [224].

Heart rate fluctuates at different frequencies. Frequency domain indices result from a power spectral analysis of consecutive RR intervals [225, 230], and quantify the extent to which different frequencies are present in heart rate fluctuations (Fig. 2). In general, oscillations are divided into different frequency ranges: high frequency (HF: 0.15–0.4 Hz), low frequency (LF: 0.05–0.15 Hz), very low frequency (VLF: 0.0033–0.04 Hz), or ultra-low frequency (ULF: ≤ 0.0033 Hz) [225, 230].

Of these frequencies, VLF is most strongly associated with all-cause mortality and incidence of arrhythmias [231, 232]. Interestingly, rather than reflecting efferent innervation, VLF appears to reflect the frequency at which cardiac afferent nerves are stimulated. This, therefore, suggests that VLF more closely reflects the cardiac state, rather than the provoked response [233, 234]. Nevertheless, out of the different spectral measurements, LF, HF, and LF:HF ratio are most often reported. While LF is often considered a reflection of sympathetic tone, it predominantly reflects baroreflex modulation of cardiac autonomic outflow [230, 235, 236]. HF oscillations, on the other hand, reflect respiration-driven vagal control of heart rate, also known as the respiratory sinus arrhythmia [230, 237]. LF:HF power/ratio is therefore not a pure reflection of sympathovagal balance and should be interpreted with caution [230, 238].

Baroreflex sensitivity

The baroreflex serves to regulate mean arterial pressure, and therefore, safeguards proper perfusion of vital organs. Cardiovascular baroreceptors are primarily found in the carotid artery sinuses and aortic arch and relay information about vascular stretch to the CNS [239]. Higher arterial pressures, which cause more stretch of the vascular wall, increase firing rate of these sensory afferent neurons, which activate glutamatergic neurons in the NTS [239, 240]. These neurons excite second-order neurons in the caudal ventrolateral medulla, which in turn release GABA, thereby inhibiting neurons in the RVLM. As central sympathetic outflow is partially derived from the RVLM, this inhibition decreases sympathetic outflow and, as a result, decreases heart rate, contractility, and blood pressure. In the setting of low blood pressures, inhibition of the neurons in the RVLM is relieved, allowing for higher central sympathetic outflow, resulting in a reflexive increase in heart rate [239, 240].

Quantification of this change in heart rate in response to an increase or decrease in blood pressure may be reflective of autonomic (dys)function. Baroreflex sensitivity (BRS), measured as the change in the RR interval per mmHg change in blood pressure, is often assessed using

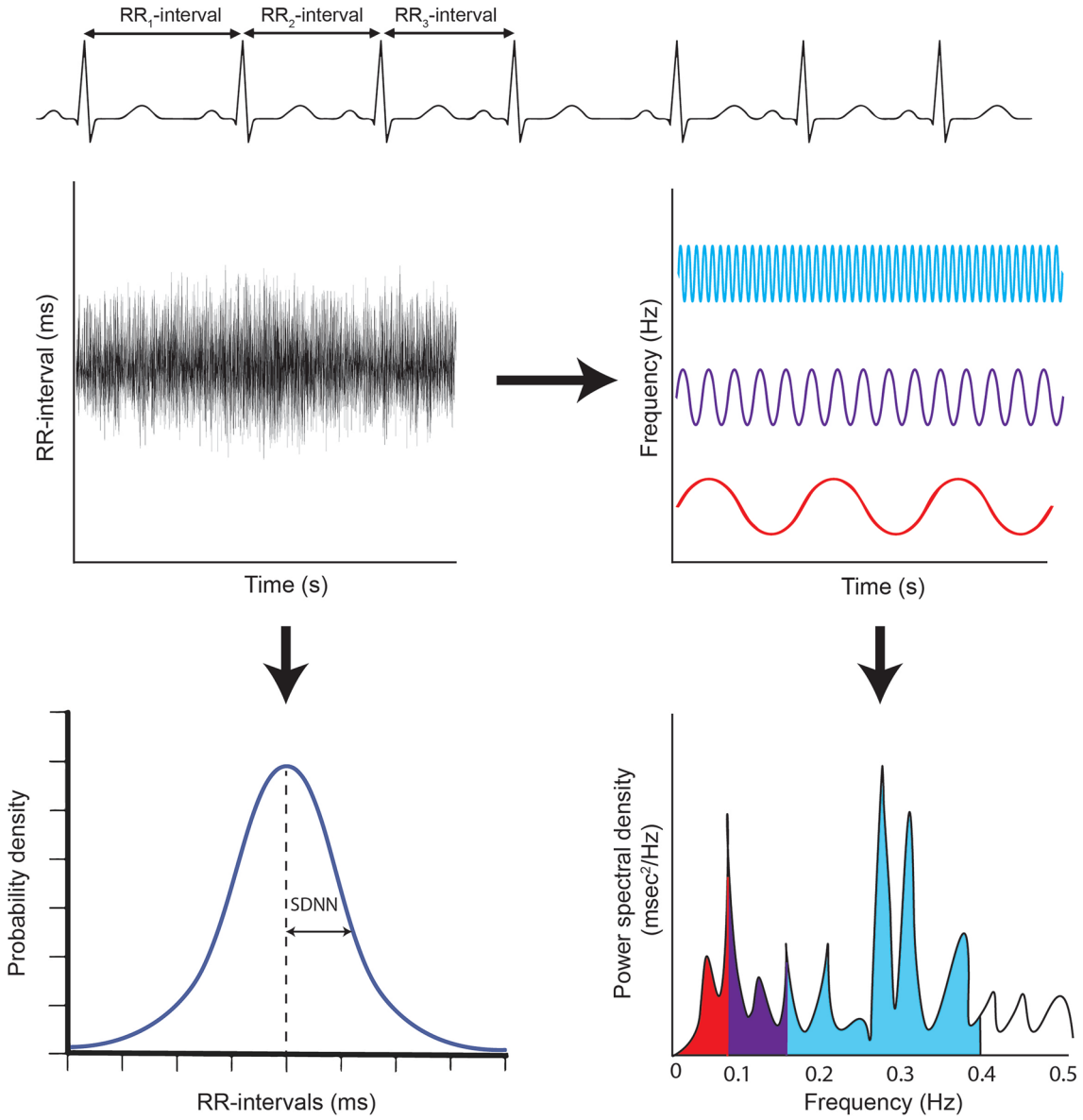

Fig. 2 Heart rate variability measures in the time and frequency domain. Heart rate variability is a measure of the beat-to-beat variability in the RR interval. Temporal domain indices, such as SDNN, quantify the extent of beat-to-beat RR-interval variability over time. SDNN reflects the standard deviation of consecutive RR intervals. Frequency domain analyses quantify the extent to which different frequencies are present in RR-interval oscillations as the power of a frequency. The different frequencies are reflective of sympathetic, parasympathetic, and/or autonomic reflex loops and, therefore, represent cardiac autonomic input

pharmacologic interventions with phenylephrine (vasoconstrictor) or sodium nitroprusside (vasodilator). As such, depending on the type of drug used, the sympathetic or parasympathetic baroreflex is tested [241]. Baroreflex can also be measured noninvasively, using finger arterial pressure measurements combined with an ECG. However, these spontaneous measurements do not correspond well with invasive measurements of BRS and have been found to be significantly inferior [241]. Alternative noninvasive methods to quantify BRS utilize neck suction/pressure or the Valsalva maneuver for activation of baroreceptors. The various methods of BRS assessment and their respective advantages and disadvantages are described in detail by La Rovere et al. [241].

Autonomic dysfunction, especially parasympathetic withdrawal in cardiovascular diseases, decreases BRS. Correspondingly, a lower BRS correlates with higher cardiovascular mortality and an increased susceptibility to ventricular arrhythmias after myocardial infarction [242] and in heart failure patients [243–245].

Heart rate turbulence

Heart rate turbulence (HRT) assesses the sequence of autonomic responses to a PVC [246]. During a PVC and the subsequent compensatory pause, less blood is ejected from the heart, causing a decrease in blood pressure. This is sensed via autonomic neurons mediating the baroreflex, which then increase their firing (early acceleration phase). This causes the blood pressure to "overshoot" and reach a higher level than before the PVC, which is subsequently sensed by the autonomic nervous system, inducing a deceleration in heart rate (late deceleration phase). This consecutive acceleration and deceleration of heart rate is quantified as the turbulence onset (TO) and the turbulence slope (TS). TO quantifies the percentage change in heart rate directly after the compensatory pause versus before the PVC. TS, on the other hand, is the maximum regression slope of the late deceleration phase (quantified using at least five consecutive RR intervals) [246]. Clinically, this measure can be extracted from Holter recordings, or be obtained through pacing-induced PVCs at 60–70% of sinus rate cycle length.

HRT has been demonstrated to be an independent predictor of cardiovascular death after myocardial infarction, as well as in congestive heart failure and idiopathic dilated cardiomyopathy [246–248]. Unfortunately, it has low sensitivity (approximately 30%), and its reliability is highly influenced by the baseline heart rate (worse with higher heart rates) [246].

Imaging modalities

Neuroimaging is a diagnostic tool that visualizes cardiac innervation. The most commonly used compound is metaiodobenzylguanidine (MIBG), a guanethidine derivative, that, upon intravenous administration, is taken up into the sympathetic nerve terminals through similar mechanisms as NE [249]. Following its endocytosis, MIBG is neither metabolized nor catabolized, and thus, accumulates intracellularly. Leveraging these properties, MIBG can be radiolabeled with a marker such as ^{123}I, thereby allowing for visualization and quantification of cardiac sympathetic nerve density and neurotransmitter reuptake. As autonomic remodeling results in less NE reuptake, more MIBG will be washed out over time. This phenomenon is quantified as the heart:mediastinum ratio (H:M). The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial assessed the utility of MIBG scintigraphy in identifying heart failure patients at increased risk for sudden cardiac death (SCD). It demonstrated that a lower H/M ratio (<1.6) significantly correlated with a higher risk of SCD [250]. Similarly, a higher H:M ratio corresponded to higher survival rates in heart failure patients [251–253]. Major limitations of this method, however, include the low spatial resolution and the dependency of the image quality on the collimator that is being used [254].

Alternative imaging compounds using positron emission tomography with NE analogs have been developed, including ^{11}C-hydroxyephedrine. In comparison to ^{123}I-mIBG, the affinity of ^{11}C-hydroxyephedrine for the norepinephrine transporter is higher, allowing for better differentiation between innervated and denervated myocardium [107, 255]. Correspondingly, positron emission photography using ^{11}C-hydroxyephedrine has been proven to adequately assess the extent of cardiac sympathetic denervation and identify patients that may be at increased risk of ventricular arrhythmias and sudden cardiac death [107]. A major difference between MIBG and ^{11}C-hydroxyephedrine is the imaging technique employed to visualize the compound. Whereas MIBG uses single photon emission computed tomography (SPECT), ^{11}C-hydroxyephedrine relies on positron emission tomography, which is less widely available.

Treatment strategies targeting the autonomic nervous system in heart failure with reduced ejection fraction and ventricular arrhythmias

Beta-blockers Beta-blockers remain the corner stone of cardiovascular treatment after myocardial injury, as they improve cardiac function in heart failure, reduce ventricular arrhythmia susceptibility, and decrease mortality [256, 257]. In the setting of heart failure, bisoprolol, metoprolol, and carvedilol have been best evaluated, reducing mortality on average by 35% [257–260].

Even though all beta-blockers impede sympathetic activity via blockade of beta-adrenergic receptors on the heart, understanding the characteristics of different beta-blockers can aid in selecting the best one in a specific situation. One of the major differences between different types of beta-blockers is their specificity for the beta-1 receptor. The first generation of beta-blockers was in general nonselective for beta-1 or beta-2 receptors, whereas second generation beta-blockers are specific for beta-1 receptors (Table 2).

Third generation beta-blockers have additional vasodilatory effects through alpha-receptor blockade or nitric oxide release (Table 2) [261]. These drugs, therefore, also lower peripheral vascular resistance and systemic blood pressure. Moreover, some beta-blockers have intrinsic sympathomimetic properties. These drugs can lower systemic blood pressure, without affecting heart rate and cardiac output. Therefore, these maybe more suitable in situations such as sinus bradycardia and/or sick sinus syndrome [262].

Beta-blockers are known to cause several adverse effects due to off-target binding in the CNS, which reduces patient compliance. These included fatigue, reduced ability to concentrate, nightmares, and/or depression [263]. Lipophilicity of a drug (which corresponds to its ability to cross the

Table 2 Commonly used beta-blockers and their characteristics

Beta-blocker	Generation	β_1-selective	α-block	ISA	Half-life (hours)	Lipophilic
Carteolol	1	No		+	6–8	
Nadolol	1	No			12–24	
Penbutolol	1	No		+	18–27	+ +
Pindolol	1	No		+ +	3–4	+ +
Propranolol	1	No			3–4	+ +
Sotalol	1	No			12	
Timolol	1	No			4–5	+ +
Acebutolol	2	Yes		+	3–4	+
Atenolol	2	Yes			6–9	
Betaxolol	2	Yes			14–22	+
Bisoprolol	2	Yes			9–12	+
Esmolol	2	Yes			9 min	
Metoprolol	2	Yes			3–4	+
Carvedilol	3	No	+		7–10	+
Celiprolol	3	Yes	+	+	4–5	
Labetalol	3	No	+		3–4	
Nebivolol	3	Yes	+ (NO)		8–27	+

NO: vasodilatory effect through increased nitric oxide. ISA: intrinsic sympathomimetic activity
+: Moderate; ++: High

blood–brain barrier) should be considered when deciding an appropriate alternative (Table 2).

Renin–angiotensin–aldosterone system inhibitors Decreased cardiac output also stimulates the release of renin by the kidneys, which subsequently leads to increases in angiotensin I and II as well as aldosterone. This systemic activation of the renin–angiotensin–aldosterone system (RAAS) further exacerbates heart failure and sympathovagal balance, but may also have direct effects on autonomic dysfunction.

Angiotensin II heightens sympathetic tone by binding to presynaptic angiotensin I receptors on sympathetic neurons, facilitating NE release [264] and inhibiting norepinephrine reuptake [265]. Moreover, angiotensin II blunts the baroreflex, most likely via reducing cardiac vagal tone [266, 267]. Additionally, CSAR is increased by increases in central angiotensin II receptors [268, 269], which can be inhibited by angiotensin I receptor antagonist losartan [270]. Hence, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists have been demonstrated to decrease plasma NE levels, improve cardiac autonomic tone as measured by ^{123}I-mIBG, and improve BRS [271–274].

Similarly, angiotensin receptor–neprilysin inhibitors (ARNIs) improve outcomes in heart failure patients, reverse cardiac remodeling, and decrease the incidence of ventricular arrhythmias and sudden cardiac death [275]. Interestingly, a more recent study has linked these effects in part to restoration of parasympathetic tone and sympathovagal balance [276], though additional studies are needed to dissect the effects of ARNIs on vagal function.

Sodium–glucose cotransporter 2 inhibitors A more novel group of drugs for patients with heart failure and a reduced ejection fraction are the sodium–glucose cotransporter 2 (SGLT2) inhibitors [257]. Their principal mechanism of action is through increasing glucose excretion in urine, thereby, causing natriuresis and osmotic diuresis, which reduces plasma volume and blood pressure. Reducing volume overload on the heart might very well improve autonomic tone, though additional mechanisms may also be present. Various studies have shown the beneficial effects of SGLT2 inhibitors on autonomic tone [277, 278], including the EMBODY trial, which reported improved autonomic parameters measured by HRV (e.g., LF:HF ratio) in patients with type 2 diabetes on SGLT2 inhibitors, 4 weeks after acute myocardial infarction [279].

Cardiac resynchronization therapy Cardiac resynchronization therapy (CRT) has become an established non-pharmacological therapy in heart failure patients with reduced ejection fraction and ventricular dyssynchrony (predominantly in the setting of left bundle branch block), reducing mortality. Reversed autonomic remodeling has been observed after CRT [257]. Cha et al. [280] reported improved H:M ratio on MIBG in CRT responders after 6 months of treatment [280]. In addition, other studies have reported improved

HRV, HRT, and BRS in CRT responders compared with nonresponders or control groups [281–284].

Cardiac sympathetic denervation Cardiac sympathetic denervation (CSD) is a permanent therapeutic approach to interrupt cardiac sympathetic efferent and afferent neurotransmission at the level of the stellate and thoracic sympathetic ganglia. In most cases, CSD is performed by surgical excision of the lower half or third of the left or bilateral stellate and T2–T4 thoracic ganglia.

Thus far, CSD has been primarily performed and evaluated as a treatment option for recurrent and refractory ventricular arrhythmias, including in patients with channelopathies (long QT syndrome and catecholaminergic polymorphic VT) and cardiomyopathy/structural heart disease [204, 285–287]. Multiple preclinical and clinical studies as well as case series have demonstrated a robust anti-arrhythmic effect for both polymorphic and monomorphic VT [288]. Additionally, a small, randomized pilot study by Conceicao-Souza et al. [289] reported improvement in LVEF and decreased cardiac morbidity in patients with New York Heart Association (NYHA) Class II or III heart failure that underwent left CSD compared with optimal medical therapy alone.

Side effects of CSD are uncommon, but include (partial) Horner's syndrome, compensatory hyperhidrosis, and neuropathy/neuropathic pain [290, 291].

Stellate ganglion block Stellate ganglion block (SGB) also aims to interrupt cardiac sympathetic outflow at the level of the stellate ganglia with the use of anesthetic agents. Hence, its effects are temporary and reversible. The block can either be achieved as a single injection or through continuous infusion upon placement of a catheter [292, 293]. The duration of the block also depends on the half-life of the local anesthetic used, such as bupivacaine or lidocaine. SGB has been described in case series as a treatment modality for electrical storm [294, 295], allowing for acute stabilization of these patients. Its applicability to other settings has not been described.

Thoracic epidural anesthesia Thoracic epidural anesthesia (TEA) has also emerged as a promising and relatively noninvasive neuromodulatory approach that was reported to decrease ventricular arrhythmia burden in small case series of patients with structural heart disease and in animal models of myocardial infarction [296–298]. Administration of an anesthetic agent in the epidural space can block both spinal afferent and sympathetic efferent signals in a reversible fashion. TEA can acutely stabilize patients with recurrent VA, allowing these patients to be bridged to more permanent therapies such as CSD, catheter ablation, or cardiac transplantation [296, 297, 299]. Its broader applicability has been limited by the need for interruption of blood thinners and its potentially unknown effects on hemodynamic parameters, as cardiac sympathetic outflow becomes significantly decreased. Additional preclinical and clinical studies are needed to shed light on the hemodynamic and electrophysiological effects of TEA in the setting of heart disease.

Renal artery denervation Both renal efferent and afferent nerves are involved in enhancing systemic sympathetic responses [300, 301]. Whereas the efferent nerves promote renal sodium reabsorption and activate the renin–angiotensin–aldosterone system, renal afferents relay their sensory information through dorsal root ganglia, increasing cardiovascular sympathetic tone [300, 301]. Disrupting this cycle by renal denervation and ablation of the renal nerves was first explored as a treatment for hypertension. Despite the promising results of the SYMPLICITY HTN-1 and -2 trials [302, 303], the SYMPLICITY HTN-3 clinical trial failed to show benefit in blood pressure regulation in the treatment arm compared with the control arm [304]. Since then, various randomized sham-controlled studies have demonstrated an overall benefit for renal nerve denervation as an antihypertensive treatment, though individual responses can still vary [305–307]. Recently, renal nerve stimulation has received increasing attention as a method of guiding adequate renal denervation [308, 309]. Renal nerve stimulation prior to ablation can help localize renal plexus; a mitigated increase in blood pressure response to stimulation post-denervation has been reported to positively correlate with long-term benefit of renal denervation [308, 309].

As autonomic dysfunction and increased sympathetic tone are cornerstones in the pathogenesis of ventricular arrhythmias, renal denervation has also been explored as an adjunctive therapeutic option for ventricular tachycardia [310]. In a canine study, bilateral renal denervation (both chemical and mechanical) after creation of myocardial infarction reduced ventricular fibrillation burden by stabilizing the electrical properties of infarct border zone [311]. Moreover, multiple case series have collectively suggested a benefit for renal denervation in patients with refractory ventricular arrhythmias [310], though randomized trials are lacking.

Baroreflex stimulation Baroreflex stimulation (BAT) involves implantation of a baroreflex stimulator in the carotid sinus, mimicking afferent signaling of increased vascular stretch and resulting in reduced central sympathetic and increased vagal outflow to the heart. Chronic bilateral baroreflex stimulation improved survival and restored autonomic tone in animal models of both ischemic and nonischemic heart failure [312, 313]. Since then, various studies have demonstrated improved morbidity and mortality in patients with advanced heart failure implanted with BAT. More specifically, BAT

improved NYHA class, quality of life, baroreflex sensitivity, and reversed left ventricular remodeling [314–317]. Notably, right-sided stimulation has been shown to cause more pronounced effects on blood pressure than left-sided stimulation or bilateral stimulation [318]. Baroreflex stimulation has been approved by the FDA in the treatment of heart failure patients (NYHA II or III) who remain symptomatic, have a left ventricular ejection fraction of 35% or lower and NT-proBNP levels below 1600 pg/mL despite optimal medical therapy, and are not eligible for CRT implantation [257].

Vagal nerve stimulation Vagal nerve stimulation (VNS) is another treatment modality currently under investigation for heart failure to increase parasympathetic outflow to the heart. Animal studies employing chronic VNS in canine models of heart failure demonstrated efficacy in improving left ventricular systolic function, decreasing plasma levels of heart failure biomarkers, and decreasing mortality [319–321]. Moreover, the first clinical trials in humans showed similar results, including improved left ventricular ejection fraction, quality of life, and NYHA class [322, 323]. However, subsequent larger, randomized, clinical trials failed to replicate these results and found no significant improvement in heart failure patients with or without VNS [324, 325]. The contradicting results in clinical benefit from VNS are largely attributed to differing stimulation parameters [326, 327], warranting further preclinical and clinical studies. Although heart failure has been the primary focus of VNS clinical trials, preclinical studies have also suggested benefit in reducing ventricular arrhythmia inducibility after chronic myocardial infarction [153].

Conclusion

Autonomic dysfunction, characterized by excessive and deleterious activation of the sympathetic nervous system accompanied by parasympathetic withdrawal and dysfunction, is inherent to the pathophysiology of many cardiovascular diseases. Mechanistic gaps, especially related to causes of vagal dysfunction and specific mediators of chronic sympathetic activation, require further investigation. Improved diagnosis of the degree of autonomic dysfunction and assessment of the extent of sympathovagal imbalance can lead to initiation and implementation of better targeted, more personalized therapies and development of novel treatments that restore cardiac autonomic tone and improve survival for patients with cardiovascular disease.

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