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The role of the autonomic nervous system in arrhythmias and sudden cardiac death

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ABSTRACT

The autonomic nervous system (ANS) is complex and plays an important role in cardiac arrhythmia pathogenesis. A deeper understanding of the anatomy and development of the ANS has shed light on its involvement in cardiac arrhythmias. Alterations in levels of Sema-3a and NGF, both growth factors involved in innervation patterning during development of the ANS, leads to cardiac arrhythmias. Dysregulation of the ANS, including polymorphisms in genes involved in ANS development, have been implicated in sudden infant death syndrome. Disruptions in the sympathetic and/or parasympathetic systems of the ANS can lead to cardiac arrhythmias and can vary depending on the type of arrhythmia. Simultaneous stimulation of both the sympathetic and parasympathetic systems is thought to lead to atrial fibrillation whereas increased sympathetic stimulation is thought to lead to ventricular fibrillation or ventricular tachycardia. In inherited arrhythmia syndromes, such as Long QT and Catecholaminergic Polymorphic Ventricular Tachycardia, sympathetic system stimulation is thought to lead to ventricular tachycardia, subsequent arrhythmias, and in severe cases, cardiac death. On the other hand, arrhythmic events in Brugada Syndrome have been associated with periods of high parasympathetic tone. Increasing evidence suggests that modulation of the ANS as a therapeutic strategy in the treatment of cardiac arrhythmias is safe and effective. Further studies investigating the involvement of the ANS in arrhythmia pathogenesis and its modulation for the treatment of cardiac arrhythmias is warranted.

1. Overview of the cardiac nervous system

Death due to cardiac arrhythmias remains a significant problem of epidemic proportions. The American Heart Association reported that in 2004, 310,000 sudden cardiac deaths occurred in the United States and about two-thirds of unexpected cardiac deaths occurred without previous recognition of cardiac disease (Rosamond et al., 2008). This leaves a significant burden on surviving family members and those who may be at risk of a sudden cardiac event. Often, cardiac arrhythmias go unnoticed and the events that trigger them are difficult to predict. Increasing evidence suggests that the autonomic nervous system (ANS) plays a role as a trigger and predisposing factor in arrhythmia pathogenesis, making it a potential therapeutic target in the treatment of cardiac arrhythmias.

The term “autonomic nervous system” (ANS) was first coined by Langley (Langley, 1921) and has been implicated in numerous conditions including abnormalities of the heart (Fig. 1A). The heart receives input from both the sympathetic and parasympathetic systems, regulating heart rate, rhythm and contractility. Sympathetic innervation to the heart originates mainly from the right and left stellate ganglia. On the other hand, cardiac parasympathetic activity is mediated through the vagus nerve which originates in the medulla. The effects of the sympathetic system are mediated primarily through the actions of the neurotransmitter norepinephrine (noradrenaline) on alpha and beta adrenergic receptors together with co-transmitters, including neuropeptide Y and galanin (Shivkumar et al., 2016). Enhanced sympathetic stimulation increases discharge of the sinoatrial node (SAN) and augments atrioventricular node (AVN) conduction leading to an increase in heart rate and contractility. The parasympathetic systems effects are mediated primarily through acetylcholine activation of muscarinic and preganglionic nicotinic receptors and results in decreased heart rate and contractility.

The distribution of sympathetic and parasympathetic innervation within the heart varies (Fig. 1B). A gradient exists in sympathetic innervation from atria to ventricles and from base to apex of the heart. The atria are more densely innervated than the ventricles, but the

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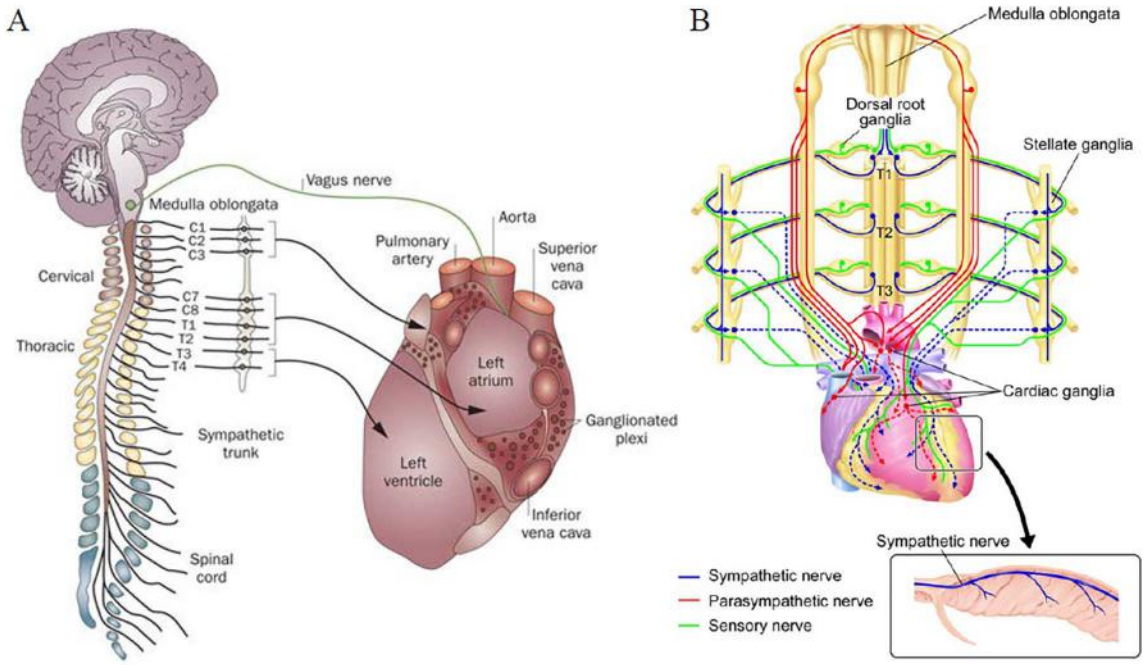

Fig. 1. Anatomy and distribution of the cardiac nervous system. A) The cardiac sympathetic ganglia consist of cervical, stellate and thoracic ganglia. The parasympathetic innervation originates from the vagus nerve. Reprinted from Shen et al., 2012 by permission from Nature Publishing Group, Copyright 2012. B) The sympathetic nerves (blue) extend from the stellate ganglia to the SAN and AVN. The parasympathetic nerves (red) extend from the vagus nerve which originates from the medulla to the base of both atria. The inset demonstrates the distribution of the sympathetic nerves in the ventricles. Reprinted from Kimura et al., 2012 by permission from Wolters Kluwer Health, Inc., Copyright 2012. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

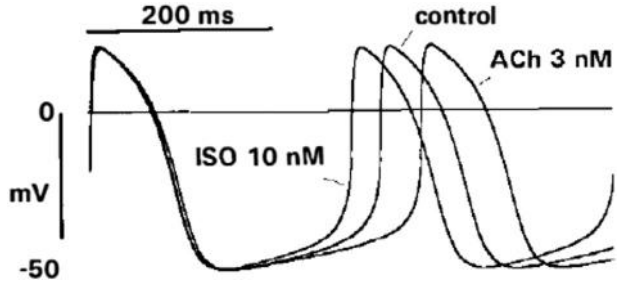

Fig. 2. Effects of isoproterenol or acetylcholine on action potential frequency of a single sinoatrial node cell. Typical action potentials of an isolated SA nodal myocyte under control conditions ("control"), in the presence of 10 nM isoproterenol ("ISO") or 3 nM acetylcholine ("ACh"). Isoproterenol, which activates the sympathetic system, increases action potential frequency whereas acetylcholine, which activates the parasympathetic system, slows action potential frequency. No effect of either neurotransmitter was seen on action potential shape or duration and was attributed to the low concentrations used. Reprinted from DiFrancesco, 1993 by permission from Annual Reviews, Copyright 1993.

ventricles are also supplied with a very thick sympathetic network at the base. Parasympathetic neurons are dispersed much more heterogeneously throughout the heart with dense innervation of the SAN and AVN, and to a lesser extent to the atria. In addition, the right ventricle is more densely innervated than the left ventricle and the left ventricular endocardium is more densely innervated than the right ventricular endocardium (Kimura et al., 2012). The intrinsic cardiac ganglia and interneurons process information from both the sympathetic and parasympathetic systems, as well as myocardial sensory neurons, and send projections to other cardiac ganglia (Armour, 1999). Imbalance between the two branches of the autonomic nervous system (sympathetic vs parasympathetic stimulation) may cause clinically relevant perturbations in cardiac physiology. Effects of the sympathetic to increase and parasympathetic nervous system to decrease the cardiac action potential frequency are demonstrated in Fig. 2. Like norepinephrine, isoproterenol activates the sympathetic nervous system through beta receptors increasing action potential frequency whereas acetylcholine, which acts primarily on the parasympathetic system, slows action potential frequency. Enhanced parasympathetic influence on the heart is generally antiarrhythmic and antifibrillatory (Vanoli et al., 1991; Lown and Verrier, 1976) while increased sympathetic influence is generally pro-arrhythmic (Schwartz et al., 1992).

2. Development of the ANS and innervation patterning play a role in arrhythmia pathogenesis

The development of the ANS is an important component in understanding autonomic pathophysiology, since an early genetic error affecting ANS development could have profound implications on autonomic cell populations (Axelrod et al., 2006). The cells of the ANS originate from the multipotential neural crest cells (Axelrod et al., 2006). These cells migrate and eventually evolve into sensory and autonomic ganglia. Several key transcription factors have been identified as critical for development of the ANS: the *MASH1* (mammalian achaete-scute homologue) and *PHOX2* (paired-like homeobox 2) genes are necessary for differentiation of uncommitted neural crest cells to the developing ANS (Sommer et al., 1995; Tiveron et al., 1996). Differentiation into functional mature neurons is incumbent on exposure to growth factors released by structures along the migratory route and within the target tissue. Nerve growth factor (NGF) in the embryonic neuron promotes migration from the neural crest and enhances maturation through neurite outgrowth. In addition to promoting cardiac neuronal survival, NGF mediates axonal growth and synapse formation during development. In the mature neuron, NGF dependence decreases but continues to enhance neurotransmitter synthesis (Thoenen and Barde, 1980). Interestingly, NGF infusion after myocardial infarction resulted in enhanced myocardial nerve sprouting (Fig. 3), and increased the incidence of ventricular tachyarrhythmias and sudden death (Cao et al., 2000). These results confirm the importance of NGF for regulating sympathetic neuron development and cardiac innervation. In addition to NGF, signaling through NT-3, which is derived from vascular smooth muscle cells, is thought to be tightly coupled to NGF in promoting sympathetic axon extension along

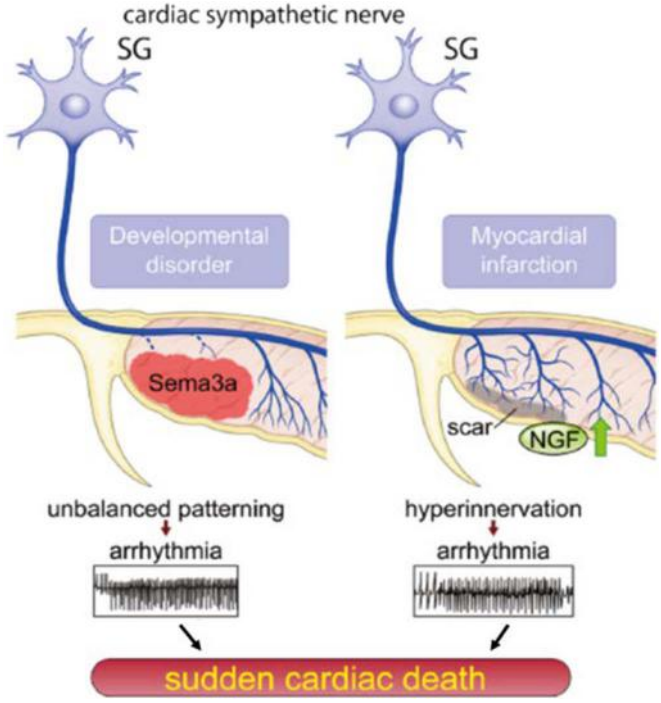

Fig. 3. Cardiac innervation patterns leading to sudden cardiac death. Left: Overexpression or under expression of Sema3a, a class 3-secreted semaphorin which acts as a potent neural chemorepellant, results in abnormalities in innervation patterning of sympathetic nerves leading to arrhythmias and sudden cardiac death. Right: Overexpression of NGF leads to a disrupted patterning of sympathetic neurons leading to hyperinnervation, arrhythmias and sudden death. Reprinted from Fukuda et al., 2015 by permission from Wolters Kluwer Health, Inc., Copyright 2015.

the vasculature (Kuruvilla et al., 2004). Parasympathetic nerve development, in contrast, is dependent on glial cell-derived neurotrophic factor signaling (Kimura et al., 2012).

Sympathetic nerve sprouting and perturbed innervation are thought to play a role in arrhythmias (Chen et al., 2007). Sema3a, a class 3-secreted semaphorin, acts as a potent neural chemorepellant, regulating axon/dendrite growth and neuronal migration (Goshima et al., 2012). Interestingly, Sema3a is strongly expressed in the developing heart and expression gradually decreases with development (Kimura et al., 2012). Sema3a is thought to act as a negative regulator of cardiac sympathetic innervation, playing a role in innervation patterning by inhibiting neural growth. Overexpression of Sema3a has been shown to lead to sustained ventricular tachyarrhythmias in mice (Fig. 3), upregulation of beta adrenergic receptor density and prolonged action potential duration. This demonstrates the importance of neurotrophic factors in promoting neuronal survival, innervation patterning and in arrhythmia pathogenesis.

3. ANS abnormalities are implicated in SIDS pathogenesis

Sudden infant death syndrome (SIDS) refers to the sudden death of an infant younger than one year that remains unexplained after a thorough investigation including autopsy, death scene investigation and clinical history review. An immature respiratory and autonomic nervous system has been implicated in SIDS pathogenesis (Moon et al., 2007). Structural and neurotransmitter alterations in the brainstem have been found in SIDS patients, consistent with autonomic dysregulation. These changes include increases in dendritic spine density, a marker of delayed neuronal maturation, and delayed maturation of synapses in medullary respiratory centers (Quattrochi et al., 1985). Polymorphisms in genes that effect ANS development (impaired autonomic regulation) including *PHOX2A*, *RET*, *ECE1*, *TLX3*, *EN1* have been reported in SIDS patients (Weese-Mayer et al., 2004).

Serotonin, a neurotransmitter, influences various autonomic functions including cardiorespiratory and circadian rhythms. Abnormalities in serotonin receptors and transporters have been found in SIDS patients and shown to affect arousal response. Polymorphisms in the serotonin transporter (5-HTT) gene, resulting in increased transporter activity and a reduction in 5-HTT concentrations at nerve endings, increased number and density of 5-HTT neurons with decreased serotonin receptors have been reported (Kinney, 2009). These alterations have been linked to functional changes in arousal pathways (e.g. cortical and subcortical) resulting in a decreased tendency to arouse from sleep in the latter part of the night when most SIDS events occur (Kato et al., 2003).

Interestingly, several associations have been reported between SIDS and inherited cardiac arrhythmia syndromes. Long QT (LQT) Syndrome is a rare inherited or acquired ion channelopathy that increases the risk of developing a polymorphic ventricular tachycardia, known as torsades de pointes, and sudden cardiac death. LQT and SIDS share similar phenotypes including prolonged QT, lower parasympathetic tone and/or sympathovagal imbalance, higher baseline heart rates, lower heart rate variability and a negative post-mortem examination (Wilders, 2012). SIDS also shares an association with Brugada Syndrome since sudden death due to Brugada typically occurs during rest or while sleeping. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), which results in potentially lethal arrhythmias typically triggered by stress or exercise, has also been associated with SIDS. During sleep, there could be sudden increases in sympathetic activation making CPVT affected infants susceptible to arrhythmias and subsequently to SIDS (Tester et al., 2007). Further, stressors such as pain, hunger, overheating and infection may provide a mechanism to trigger a lethal cardiac event in infants who are positive for genetic mutations implicated in CPVT such as *RYR2*. Interestingly, in addition to RYR2, mutations implicated in LQT such as *KCNQ1* and *KCNH2*, as well as, *SCN5A* in Brugada, have been reported in SIDS cases (Wilders, 2012). These results indicate that disruption of the ANS and cardiac ion channel-related mutations may contribute to SIDS.

4. ANS imbalance can trigger or predispose to cardiac arrhythmia

ANS dysfunction has a significant impact on the induction and maintenance of atrial and ventricular arrhythmias (Fukuda et al., 2015; Zipes, 2015). Enhanced sympathetic drive can exacerbate the harmful pre-existing effects of cardiac conditions including ischemia, dilated cardiomyopathies, or underlying rhythm abnormalities to initiate life-threatening arrhythmias (Fukuda et al., 2015; Shen and Zipes, 2014). Receiving input from both the sympathetic and/or parasympathetic inputs, the intrinsic cardiac nervous system plays an important role in regulating local atrial and ventricular function (Ardell et al., 2016). A deeper understanding of the role that the ANS plays in arrhythmia pathogenesis may offer potential ANS targets for both prevention and treatment of arrhythmias (Ng, 2016). A diagram summarizing the arrhythmogenic effects of the sympathetic and parasympathetic system on cardiac electrophysiology are shown in Fig. 4.

4.1. Atrial fibrillation

The ANS is a potent modulator of atrial fibrillation (AF) (Chen et al., 2014), which is the most common cardiac arrhythmia, affecting approximately 2.3 million individuals in the United States (Shen and Zipes, 2014). Several studies have described enhanced ANS activity in AF pathogenesis including simultaneous sympathetic and parasympathetic firing as inducing AF (Tan et al., 2008; Shattock and Tipton, 2012). Further support for this relationship came from studies where the stellate ganglia and vagus nerve were ablated resulting in AF elimination (Tan et al., 2008). The underlying mechanism attributed to AF induction was increased forward Na^{2+}/Ca^{2+} exchanger current contributing to transient calcium triggering (Patterson et al., 2006).

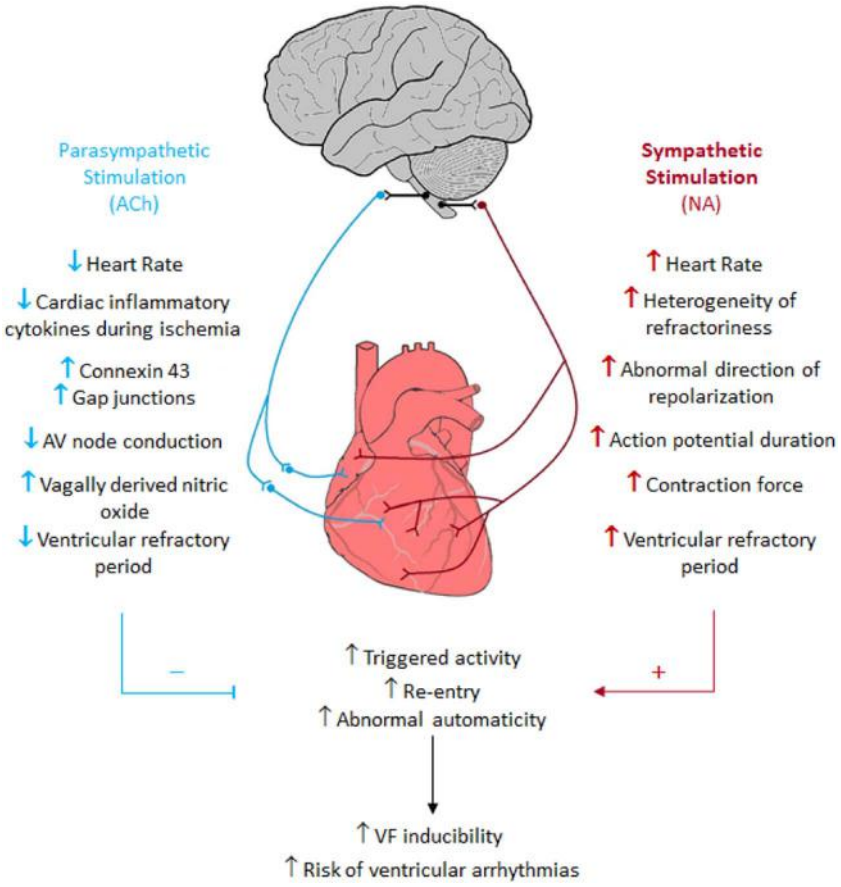

Fig. 4. Arrhythmogenic effects of the sympathetic and parasympathetic nervous system on the heart.

This is evident in the pulmonary veins which are an important focal point in the initiation of AF (Haïssaguerre et al., 1998). Interestingly, increased vagal tone and subsequent frequent premature atrial complexes lead to atrial fibrillation in athletes (Goudis et al., 2015). Similarly, atrial flutter is thought to result from increased vagal tone and is more common than AF in athletes (Calvo et al., 2012).

Although the extrinsic nervous system has a role in AF pathogenesis, data also indicate a role for the intrinsic nervous system acting alone in generating AF. The intrinsic cardiac ANS consists of large ganglionated plexi (GP) associated with an extensive neural network of smaller groups of ganglia and their axons within the parenchyma of the atria and ventricles. Ablating the GP disconnects the intrinsic cardiac autonomic nervous system from the extrinsic nervous system. GP (right-side) ablation results in a temporary increase in atrial effective refractory period (AERP), reinnervation (increases in sympathetic and parasympathetic nerves also known as nerve sprouting), and spontaneous occurrence of atrial fibrillation and atrial tachycardia (Oh et al., 2006; Sakamoto et al., 2010; Mao et al., 2014). Autonomic remodeling may be part of the atrial substrate for AF (Gould et al., 2006). Sympathetic hyperinnervation induced by infusion of nerve growth factor or subthreshold electrical stimulation of the left stellate ganglion (LSG) in a canine model led to atrial nerve sprouting and atrial tachyarrhythmias (Swissa et al., 2005). Accordingly, modulation of these extra-cardiac neural structures may be a potential therapeutic option in the treatment of cardiac arrhythmias.

Catheter ablation as a treatment for AF such as pulmonary vein isolation (alone or with extended lesion lines) or pulmonary vein isolation with GP ablation tend to lead to more repeat procedures with diminishing returns (Bertaglia et al., 2010; Weerasooriya et al., 2011). Better treatments for AF include low level nerve stimulation applied at the auricular branch of the vagus nerve (the tragus of the outer ear), which can consistently suppress AF (Yu et al., 2013; Stavrakis et al., 2015).

4.2. Ventricular tachycardia or fibrillation (VT/VF)

Disruption of the ANS, including increased sympathetic drive, has been implicated in ventricular arrhythmia pathogenesis. Increased sympathetic activity was found to precede the onset of ventricular tachyarrhythmias in humans by 30 min (Shusterman et al., 1998). VF and sudden cardiac death were immediately preceded by spontaneous sympathetic nerve discharge from the left stellate ganglion in a canine model of sudden cardiac death (Zhou et al., 2008).

Nerve sprouting is also associated with VT/VF and sudden cardiac death. Patients with a history of VT/VF had augmented sympathetic nerve sprouting, predominantly in the border of the normal myocardium and scar tissue, as compared to patients with similar structural heart disease but no arrhythmias (Cao et al., 2000). Similarly, performing ^{131}-I MIBG scans in these patients suggest that heterogeneity of sympathetic innervation correlates with ventricular arrhythmia risk (Fallavollita et al., 2014). Rabbits on a high cholesterol diet developed myocardial hypertrophy and sympathetic hyperinnervation without coronary artery disease and had an increased incidence of VF (Liu et al., 2003). Animal studies have also shown that targeted ablation of these innervated areas around scar tissue may lead to either a decrease in the rate of or inability to induce ventricular arrhythmias (Martins, 1985). These studies strongly implicate sympathetic hyperactivity and heterogeneous sympathetic nerve sprouting or hyperinnervation as associated with incidence of VT/VF.

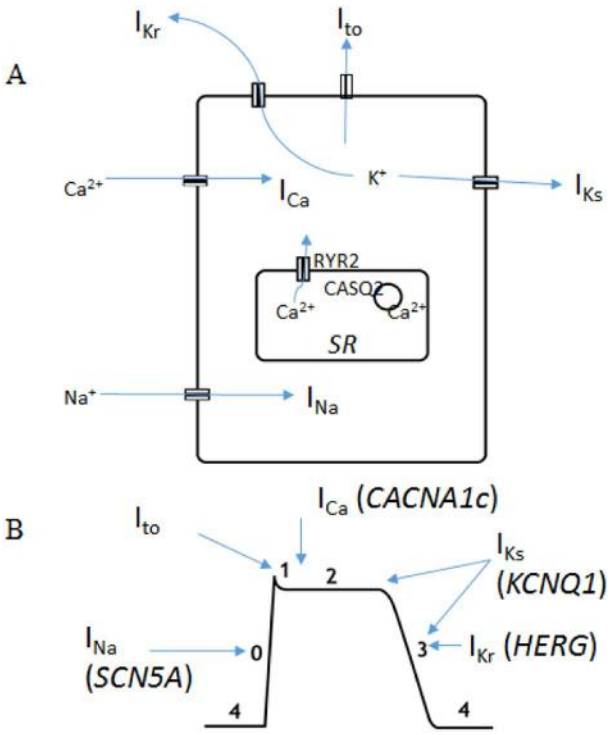

Fig. 5. A) The cardiac myocyte and ion channels regulating Na^{2+} and Ca^{2+} influx and K^+ efflux. Note the ryanodine receptor (RyR2) which facilitates calcium exit from the sarcoplasmic reticulum (SR), and calcium binding protein, calsequestrin (CASQ2), which stores calcium in the SR, implicated in CPVT pathogenesis, are located within the SR. B) The cardiac action potential consists of five phases: 0 = upstroke which is predominantly due to influx of sodium (I_{Na}), 1 = early repolarization attributed to the transient outward K^+ current (I_{to}), 2 = plateau due to inward calcium current (I_{Ca}) followed by the delayed rectifier current (I_{Ks}), 3 = final repolarization due to I_{Ks} and the delayed rectifier potassium channel (I_{Kr}) and 4 = resting potential, largely mediated by the inward rectifier potassium channel, I_{K1} (not shown). Note the genes in parentheses are implicated in ion channelopathies.

4.3. Inherited arrhythmia syndromes

The inherited arrhythmia syndromes, often referred to as cardiac ion channelopathies, represent a group of syndromes caused by unique genetic abnormalities particularly in ion channels of the heart. A schematic indicating the ion channels implicated in some of the common ion channelopathies and their relative impact on the ventricular action potential is shown in Fig. 5. Many of these inherited arrhythmia syndromes share similar clinical presentations including life-threatening arrhythmias and sudden cardiac death in the absence of any structural defects. Inherited arrhythmia syndromes account for a significant proportion of unexpected death in young and apparently healthy individuals. The prevalence of inherited arrhythmia syndromes, such as LQT Syndrome and CPVT, is estimated to be 1 per 2500 individuals (Kaltman et al., 2011). However, despite considerable advances in our understanding of these defects, it remains unclear why many individuals with the same genetic defect manifest the disease differently; it is conceivable that the autonomic background in which the deficit is manifest could be an influencing factor. Indeed, intravenous sympathomimetic or parasympathomimetic drugs are commonly used to unmask the phenotype on the ECG and in precipitating arrhythmias. This indicates that neural influences may be highly conducive to arrhythmias in inherited arrhythmia syndromes and are an important component in risk stratification.

4.3.1. Long QT syndrome

LQT is characterized by a prolonged QT interval (also known as corrected QT interval or QT_c) and risk of developing polymorphic VT causing sudden cardiac death. In normal individuals, sympathetic stimulation shortens the ventricular action potential and hence the QT interval. In contrast, in LQT Type 1 (LQT1) for example, mutations in *KCNQ1* result in a 50% reduction in basal levels of the adrenergic sensitive I_{Ks} current (i.e. loss-of function mutation) which is essential for repolarization during increases in heart rate (Porta et al., 2015). I_{Ks} is under control of the sympathetic nervous system and when the *KCNQ1* channel is disrupted, the channel is not properly regulated and there is imbalance in control of the ventricular action potential, resulting in a prolonged action potential and high risk of arrhythmias (Moss and Kass, 2005). LQT1 patients develop a prolonged QT interval and are at high risk for cardiac events during exercise or increased sympathetic activity (Moss et al., 2007). Interestingly, in a study of holter monitor data from LQT1 patients by Porta et al., 2015, including RR and QT intervals, low frequency and high frequency power, LQT1 asymptomatic mutation carriers had a higher LF over QT interval indicative of greater sympathetic control compared to symptomatic mutation carriers. These results would imply a greater ability of asymptomatic LQT1 mutation carriers to adapt QT duration to rapid changes in heart rate (Porta et al., 2015). Similarly, LQT Type 2 (LQT2) patients carry mutations in *HERG* which result in defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) (Moss and Kass, 2005). LQT2 patients develop a prolonged QT interval and are at risk of cardiac events during physical exercise and stressful or startled conditions. In contrast, LQT Type 3 (LQT3) is due to mutations in *SCN5A* which result in defects in the major cardiac sodium channel (I_{Na}) (Moss and Kass, 2005). Mutations in *SCN5A* lead to the reopening of sodium channels (i.e., gain-of-function), thereby enhancing the inward plateau current and prolonging repolarization. *SCN5A* mutations carriers are at greatest risk of cardiac events during rest (bradycardia) when sympathetic activity is expected to be low (Moss and Kass, 2005). These results indicate that autonomic susceptibility to arrhythmias differs amongst the LQT syndromes and is dependent upon the underlying ion channel subtype that is affected; I_K in LQT1/LQT2 vs I_{Na} in LQT3.

4.3.2. Brugada syndrome

Brugada syndrome patients may carry mutations in *SCN5A* which result in a loss-of-function in the sodium channel (I_{Na}). *SCN5A* mutations implicated in Brugada Syndrome are transmitted in an autosomal dominant pattern with incomplete penetrance, resulting in VT/VF and potentially sudden cardiac death. Arrhythmic events in Brugada Syndrome occur more frequently during sleep or at night (Matsuo et al., 1999). In addition to the reduced I_{Na}, factors characteristic of sleep, including low sympathetic activity, high parasympathetic activity and bradycardia, increase the transient outward current (I_{to}) exacerbating the defect in the early phase of the action potential, leading to arrhythmias in Brugada Syndrome (Morita et al., 2009). Brugada patients display a heterogeneous pattern of cardiac sympathetic innervation (Kostopoulou et al., 2010). Moreover, significantly lower levels of norepinephrine were found in cardiac biopsies of Brugada patients compared to controls, which may lead to an imbalance in sympathovagal tone and subsequent development of arrhythmias (Paul et al., 2011).

4.3.3. CPVT

CPVT is a rare, inherited arrhythmia syndrome most commonly due to a gain-of-function mutation in the *RyR2*. A rare form of autosomal recessive CPVT results from a loss-of-function mutation in calsequestrin 2 gene (*CASQ2*). In both cases, intracellular calcium levels rise to inappropriately high levels particularly during sympathetic stimulation, which further increases the function of the RyR2 and increases calcium uptake into the SR, increasing the available pool of Ca^{2+} for subsequent release. Characteristics of CPVT include a normal resting ECG, with bidirectional or polymorphic VT occurring with increased sympathetic activity such as during stress or exercise and an absence of

structural cardiac abnormalities. If untreated, CPVT can lead to delayed after depolarizations, ventricular arrhythmias, syncope and sudden death. The most common first line therapy for CPVT is β-blockers; however, a significant proportion of patients continue to experience symptoms and require further treatments including flecainide, which blocks I_{Na} and *RyR2* (Watanabe et al., 2009), implantable cardioverter defibrillators (ICDs) and left cardiac sympathetic denervation (LCSD) (Roston et al., 2015; van der Werf et al., 2012). High sympathetic tone is likely the basis for CPVT in these patients. However, sinus node dysfunction has also been reported in CPVT patients (Glukhov et al., 2015) and atrial pacing may be an effective therapeutic strategy for preventing ventricular arrhythmias during exercise for CPVT patients (Faggioni et al., 2013).

5. Evaluation of autonomic function may be beneficial in patients at risk of sudden cardiac death

Improved risk stratification techniques that identify individuals at high risk for sudden cardiac death could have a substantial impact in saving lives (Ilkhanoff and Goldberger, 2012). An array of domains needs to be considered including epidemiology and risk marker identification (Goldberger et al., 2014). Evaluation of the ANS has gained attention due to the limitations of only using left ventricular ejection fraction as a marker of sudden cardiac death (Fukuda et al., 2015). Also, improved understanding of the pathophysiology of sudden cardiac death may help identify risk predictors and consideration of special populations that may benefit from discrete risk stratification approaches. For example, in a study by Billman et al., the subset of canines that exhibited the greatest increase in heart rate in response to baroreflex challenges proved to be resistant to ischemia-induced arrhythmias (Fig. 6; Billman et al., 1982). These results demonstrate a difference in autonomic control of cardiac baroreflex responses in the two subpopulations: susceptible and resistant (Billman, 2006).

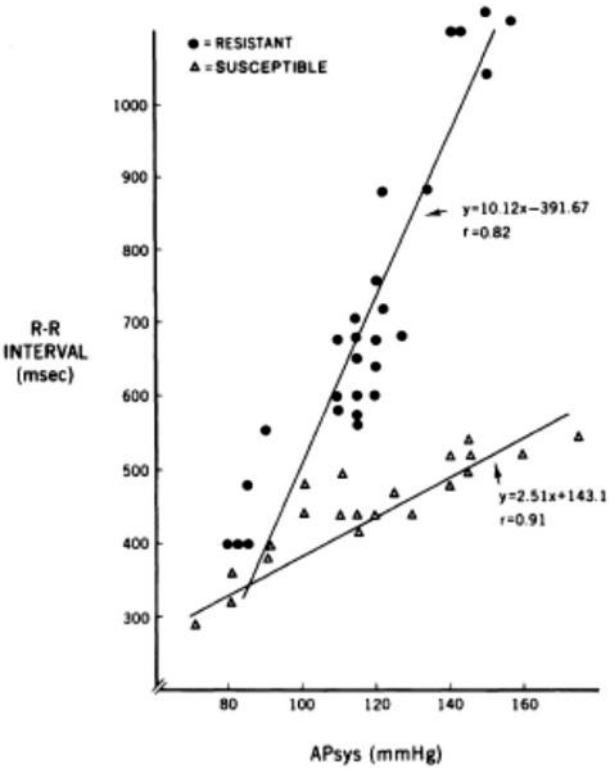

Fig. 6. RR interval vs systolic arterial pressure (APsys) in dogs after ischemia-reperfusion post myocardial infarction. A subset of dogs that exhibited the greatest increase in heart rate in response to baroreflex challenges proved to be resistant to ischemia-induced arrhythmias. Reprinted from Billman et al., 1982 by permission from Wolters Kluwer Health, Inc., Copyright 1982.

5.1. Measures of ANS function are associated with arrhythmia risk

The simplest measure of autonomic function is to evaluate resting heart rate, which is thought to predominantly reflect parasympathetic tone. Bradycardia is associated with a lower incidence of arrhythmias including in endurance athletes (Myers et al., 1974; Matelot et al., 2016). Heart rate variability (HRV), which measures spontaneous beat-to-beat changes in heart rate with components generated by both sympathetic and parasympathetic influences, has been the most extensively investigated measure of cardiac autonomic function. HRV is a measurement of the normal-normal (N-N) interval (period between the QRS complex) where low frequency (LF) components of variability correspond to sympathovagal activity and high frequency (HF) components correspond to parasympathetic or vagal activity. Overall, increased HRV is associated with improvements in morbidity and mortality (Reed et al., 2005). Studies have shown that HRV is an accurate predictor of mortality post myocardial infarction (MI) (Reed et al., 2005). However, the poor specificity of HRV to predict sudden cardiac death due to VT/VF may limit its use in risk stratification (Deyell et al., 2015). Heart rate turbulence (HRT) has been evaluated as another non-invasive and reproducible measure of autonomic function (Deyell et al., 2015). HRT quantifies the short-term variation in heart rate after a spontaneous ventricular premature beat and is closely linked to baroreceptor sensitivity (blood pressure changes), another measure of autonomic function. However, unlike most assessments of baroreceptor sensitivity, HRT requires no intervention because it can be measured from ECG recordings alone. A meta-analysis in patients with non-ischemic dilated cardiomyopathy found that none of the autonomic markers (HRV, HRT, or baroreceptor sensitivity) were predictive of sudden cardiac death-VT/VF (Goldberger et al., 2014). This may be due the underlying disease pathology, i.e. ischemic vs non-ischemic or to the focus of these autonomic markers on the sinus node rather than the disturbed autonomic function of the ventricles occurring in VT/VF (Deyell et al., 2015).

ANS changes in patients with genetically-based cardiac diseases can pose an increase in risk for sudden cardiac death. Hyperactive ANS reflexes leading to abrupt RR interval changes in either direction appear to pose an increased risk in LQT1 patients with genetic mutations that result in impaired I_{Ks} currents; this renders them unable to adapt their QT interval to abrupt heart rate changes (Schwartz et al., 2008). In general, regional abnormalities in cardiac sympathetic innervation are associated with increased arrhythmia risk. Imaging of the norepinephrine analog iodine123 meta-iodobenzylguanidine, can be used to generate an ^{123}-I MIBG defect score which provides a means for assessing the activity of cardiac sympathetic nerves, and has been shown to independently predict ventricular arrhythmias causing appropriate ICD shocks (Boogers et al., 2010). A combination of traditional ANS markers with imaging techniques (PET and SPECT) may provide a more promising risk predictor. Other studies are in support of this notion. In a prospective Prediction of Arrhythmic Events with Positron Emission Tomography (PARAPET) study of patients with ischemic cardiomyopathy receiving an ICD, the amount of viable, denervated myocardium was independently predictive of the development of VT or arrhythmic death (Fallavollita et al., 2014). Also, the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study of patients with ischemic and nonischemic LV dysfunction demonstrated that SPECT assessment of global cardiac sympathetic innervation was predictive of arrhythmic events and of heart failure progression (Jacobson et al., 2010).

5.2. Evaluation of the ANS

Evaluation of cardiac autonomic function in humans using simple non-invasive techniques is challenging and specific autonomic tests that

distinguish the risk of arrhythmic vs asystolic sudden cardiac death are desirable but not developed (Wellens et al., 2014). Cardiac autonomic function tests predominantly include evaluation of heart rate and its variability or determination of cardiovascular responses to provocation (such as active standing, passive head-up tilt test, metronomic or deep breathing, the Valsalva manoeuvre, baroreflex stimulation, responses during and in recovery after exercise and other autonomic stressors). However, there is a lack of consensus on the most appropriate assessments for clinical cardiac risk assessment and poor standardisation of assessment techniques- in many cases the reproducibility, sensitivity and specificity is uncertain.

Autonomic function can also be assessed from heart rate recovery after exercise which has prognostic significance for both total and sudden cardiac mortality (Wellens et al., 2014). There is a lack of data on the predictive value of autonomic tests or which combinations of tests would be most appropriate for various clinical conditions. It is important to consider that the risk prediction power of an ANS test increases under provoked conditions as compared to studying baseline ANS function. Furthermore, different ANS parameters as risk predictors need to be evaluated prospectively (Deyell et al., 2015).

6. ANS modulation as a treatment for arrhythmias

Despite medications, ICD and ablation, a significant proportion of patients with heart disease continue to experience arrhythmias and remain at risk of sudden death (van der Werf et al., 2012). In general, conditions/activities that promote high vagal tone, like exercise training, protect against cardiac mortality (Billman, 2009). There is growing interest in utilizing interventional procedures that are aimed at modulating sympathovagal balance (Ardell et al., 2016; Shivkumar et al., 2016; Hou et al., 2016). A summary of neuromodulation strategies is shown in Fig. 7. One of the advantages of autonomic therapy is that the cardiac nervous system exhibits memory, thus efficacy increases with time (Ardell et al., 2014, 2016).

6.1. Left cardiac sympathetic denervation

In certain situations, such as in the case of beta blocker breakthrough, intolerance to pharmacotherapy, and history of ICD shocks, left cardiac sympathetic denervation (LCSD) is considered a viable treatment option for patients who experience VT/VF events (Collura et al., 2009; Schwartz, 2014). LCSD prevents norepinephrine release in the heart and raises the threshold for VF without impairing myocardial contractility or reducing HR (Cho, 2016; Schwartz, 2014).

Reports have shown a QT attenuating effect after denervation (Cho, 2016; Costello et al., 2015). Investigation of LCSD in the largest cohort of LQT Syndrome patients studied (n = 147) indicated that only 46% of patients remained symptomatic after the procedure and the number of annual cardiac events in these patients decreased by up to 91% (Schwartz et al., 2004). LCSD was not found to be effective in LQT8, where mutations in *CACNA1C* have been implicated (Olde Nordkamp et al., 2014). Vagal withdrawal rather than sympathetic activity may be responsible for the lack of efficacy of LCSD in LQT8 (Olde Nordkamp et al., 2014). For CPVT patients who underwent LCSD, the number of symptomatic patients and annual incidence of cardiac events decreased after LCSD (Cho, 2016; De Ferrari et al., 2015; Hofferberth et al., 2014; Olde Nordkamp et al., 2014). These results highlight the significance of complete denervation for prevention of future cardiac events.

LCSD-related complications include refractory ventricular arrhythmias, spontaneous resolving pneumothorax, and transient Horner Syndrome (Cho, 2016; Schneider et al., 2013). Chronic T-cell mediated inflammation in areas of excised stellate ganglia in LQT/CPVT patients who underwent LCSD has been reported, this may boost adrenergic activity and either trigger or enhance arrhythmias in these patients (Rizzo et al., 2014). LCSD is not always an effective prevention strategy for syncope and ventricular arrhythmias in the setting of LQT or CPVT, including pediatric populations (Costello et al., 2015). ICDs are often chosen as a preferable treatment option as opposed to LCSD due to the poor predictive value of LCSD therapy and potential for sudden death in young patients.

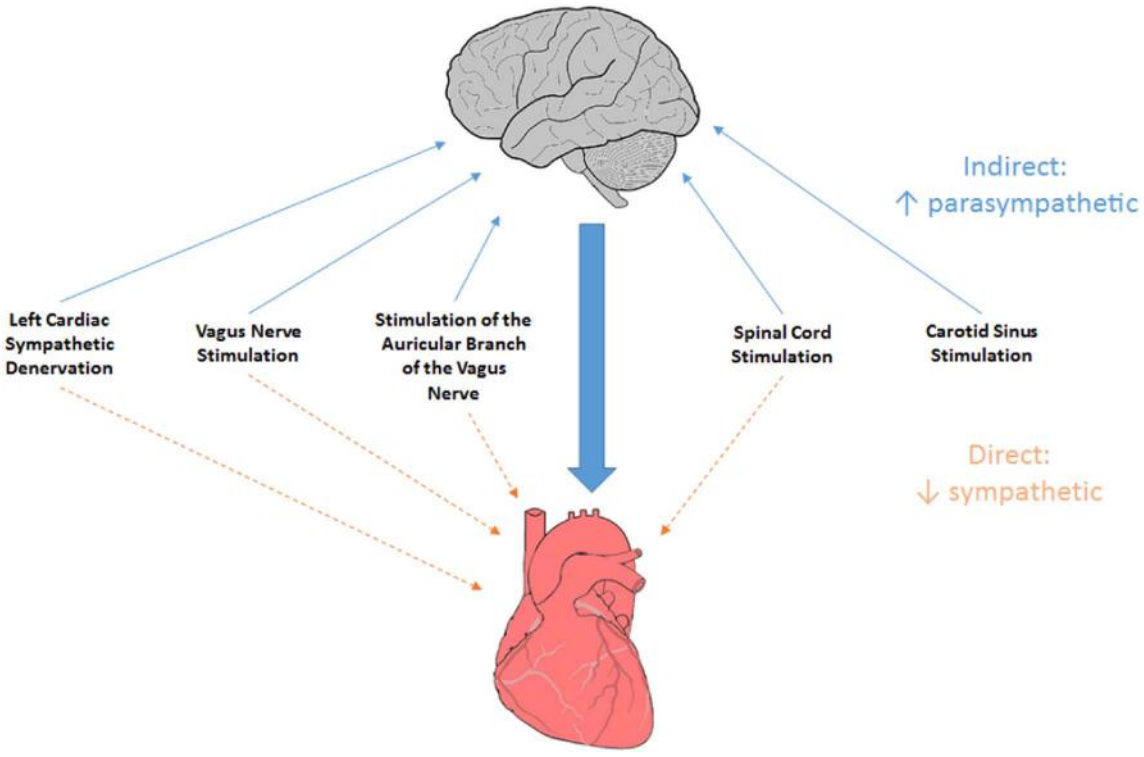

Fig. 7. Various neuromodulation strategies. Solid arrows indicate indirect approaches to increase parasympathetic activity on the heart while dashed lines indicate direct approaches to decrease sympathetic activity on the heart. The thick arrow denotes that the brain plays a major role in processing these neuromodulating strategies to alter the heart's activity. Adapted from Hou et al., 2016 by permission from Elsevier, Copyright 2016.

6.2. Vagus nerve stimulation

Studies have reported the anti-arrhythmic potential of vagal nerve stimulation (VNS) (Billman, 2006; Zipes, 2015). Increased parasympathetic activity coupled with antagonism of sympathetic stimulation of the heart leads to reduced heart rate and prolonged action potential duration (Fukuda et al., 2015). VNS induced slowing of sinus rate is dependent on the intensity of stimulation; moderate intensity stimulation is thought to be within the therapeutic range (Zhang and Mazgalev, 2011). Low level VNS is reported to reduce ventricular arrhythmic episodes, including PVCs and spontaneous VT/VF, and limits infarct size, during ischemia-reperfusion post myocardial infarction (De Ferrari and Schwartz, 2011). In addition to a reduction in heart rate and normalization of sympathetic inputs to the heart, VNS suppresses pro-inflammatory cytokines, preserves connexin 43 proteins during ischemia, inhibits the opening of the mitochondrial permeability transition pore, normalizes nitric oxide signaling pathways, and suppresses oxidative stress and cellular apoptosis (Ardell et al., 2016; Zhang and Mazgalev, 2011; De Ferrari and Schwartz, 2011). This data indicates that VNS can modify the underlying pathophysiology of heart disease.

Several clinical studies investigating the safety and efficacy of vagal nerve stimulation for the treatment of heart failure and AF have been conducted (Ardell et al., 2016; Shivkumar et al., 2016). A left-sided vagal stimulation study for the treatment of heart failure, where patients were fitted with a vagal neurostimulator system, the CardioFit System, resulted in improved quality of life, exercise capacity, LV ejection fraction, and LV systolic volumes up to 1 year after treatment. The Autonomic Regulation Therapy for the improvement of Left Ventricular Function and Heart Failure Symptoms (Anthem-HF) trial investigated autonomic regulation therapy (ART) and compared right vs left vagal nerve stimulation. Results indicated a modest trend towards greater efficacy for right-sided stimulation, with improvements persisting for one year after treatment. No significant benefits were observed in Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF) and the lack of benefit of vagal nerve stimulation in this clinical study was attributed to the inappropriate patient selection and stimulation parameters used. The first clinical trial investigating the effects of vagal stimulation for the treatment of AF indicated that 1 h of low level tragus stimulation, a less invasive procedure stimulating the auricular branch of the vagus nerve (ABVN), led to prolonged atrial effective refractory period, decreased AF and a reduction in proinflammatory cytokines with minimal adverse side effects (Stavrakis et al., 2015; Zhang and Mazgalev, 2011). These studies demonstrate the safety and feasibility of vagal nerve stimulation in the treatment of heart failure and AF.

6.3. Spinal cord stimulation

Spinal cord stimulation (SCS) has been used extensively for the treatment of refractory angina pectoris but data indicate that SCS also suppresses atrial and ventricular arrhythmias (Ardell et al., 2016). SCS minimizes sympathetic reflex responses to stress (Ardell et al., 2016). Studies have shown SCS results in a reduction of VT/VF episodes by up to 100% (Grimaldi et al., 2012; Wang et al., 2015; Odenstedt et al., 2011). The study, Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF), a randomized multicenter, single blind trial in patients with systolic heart failure, failed to show improvement in left ventricular function with SCS cycled for 12 h on and 12 h off (Zipes et al., 2016). In contrast, the Spinal Cord Stimulation Heart study, also a multi-center trial of patients with heart failure, found that continuous T1-T3 SCS improved NYHA classification, quality of life, left ventricular end systolic volume, and peak oxygen consumption (Tse et al., 2015). These results demonstrate the safety of SCS for the treatment of arrhythmias and heart failure. The mechanisms by which SCS is beneficial are thought to be through restoration of sympathetic and parasympathetic imbalance associated with reduced sympathetic modulation as supported by the reduction in heart rate variability (Grimaldi et al., 2012), and inhibition of the left stellate ganglion (Wang et al., 2015). SCS may also reduce substrate vulnerability since SCS also significantly reduced T wave alternans (Grimaldi et al., 2012). Such studies indicate that SCS is safe and therapeutic in the prevention of arrhythmias.

6.4. Carotid sinus stimulation

The carotid baroreflex plays a critical role in blood pressure regulation via modulation of the sympathetic tone. The premise for carotid sinus stimulation (CSS) therapy is that stimulation of the carotid sinus induces afferent baroreflex firing to the nucleus of the solitary tract, which is interpreted as an increase in blood pressure. This results in a reflex decrease in sympathetic stimulation with a corresponding reflex augmentation in parasympathetic activity, associated with reductions in blood pressure and heart rate. In ischemia, low level carotid sinus stimulation led to a reduction in PVCs and VT/VF (Liao et al., 2014; Sheng et al., 2016). The potential mechanisms whereby low level CSS exerts its protective effects against ventricular arrhythmias are thought to be through sympathetic withdrawal, increased vagal action, and inhibition of inflammatory oxidative stress and apoptosis (Liao et al., 2014; Sheng et al., 2016).

Several clinical trials have been performed to evaluate the safety and efficacy of carotid sinus stimulation for the treatment of drug resistant hypertension and heart failure. Patients with drug resistant hypertension implanted with a carotid sinus stimulator device (Rheos system) had sustained reductions in blood pressure up to four years after treatment (Scheffers et al., 2010) and regression of left ventricular hypertrophy (Bisognano et al., 2011a). In the Rheos Pivotal Trial, a double-blind, randomized, prospective multicenter, placebo-controlled Phase III clinical trial, baroreflex activation therapy was found to be safe and led to lowered blood pressure for up to 12 months in patients with resistant hypertension (Bisognano et al., 2011b). A miniaturized, second-generation device, the Barostim neo, was designed to reduce surgical procedure time, facial nerve complications and improve efficacy (Victor, 2015). This second-generation device is in early-phase clinical trials but data indicate safety and efficacy for the treatment of heart failure (Victor, 2015). Overall, clinical results indicate that carotid sinus stimulation is safe and effective for the treatment of heart disease.

7. ANS modulation to prevent sudden death: Complexity and future perspectives

Increasing evidence indicates that modulation of the ANS is an effective therapeutic strategy for the treatment of arrhythmias, while preserving basic integrated reflex control of the heart (Fukuda et al., 2015). The ANS is complex and clinical manifestations of ANS disorders can be varied. Clinical history alone may not be sufficient for determining the underlying cause; specific autonomic testing may be required. As the validity of autonomic tests has not been standardized in differing populations, this represents a barrier to implementing these diagnostic tools. Also, many of the ANS function tests cannot be administered to the pediatric patient. In this case, non-invasive quantitative tests that require minimal participation and cooperation are preferred. There also appears to be modifier genes affecting the response to autonomic stimuli, increasing risk for sudden death (Myerburg, 2015). This provides a reasonable direction for future studies, focusing on individual risk prediction by modifier genes.

Part of the limitation in our understanding of the ANS has been our inability to identify ways to target the ganglia without injuring the underlying myocardium. Also, treatment for one ANS system may provoke perturbations in another. Difficulty in improving cardiac cholinergic neurotransmission pharmacologically has made interventional procedures aimed at restoring sympathovagal balance an attrac-

tive therapeutic strategy (Ardell et al., 2016). Although much of the published work to date is limited to animal studies, initial studies on spinal cord stimulation, vagal nerve stimulation and carotid sinus stimulation appear promising (see Sections 6.2, 6.3 and 6.4). However, due to small patient numbers in these studies, data should be interpreted with caution. As technology to improve the safety of autonomic modulation techniques evolves, the opportunities for larger scale studies aimed at determining efficacy, optimization of stimulation parameters, and patient selection and standard of care will likely progress (Kapa et al., 2016).

8. Conclusion

The ANS comprises a complex series of interacting influences that directly impacts the cardiovascular responses to physiological stimuli, and plays a major role in the pathogenesis of cardiac arrhythmias and sudden death. Deciphering the interplay between sympathetic and parasympathetic systems will lead to a better understanding of the pathophysiology underlying several different types of cardiac diseases including cardiac arrhythmias. In turn, recognizing the levels at which one could directly impart an effect on the ANS may offer novel methods of regulation. This has the potential to treat a variety of cardiac diseases and prevent sudden death. Thus, basic, translational, and clinical research on the ANS is still needed in order to validate current and future innovations in the treatment of cardiovascular diseases.

Conflicts of interest

None.

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