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The Role of the Autonomic Nervous System in Sudden Cardiac Death

Marmar Vaseghi and **Kalyanam Shivkumar**
From the Division of Cardiology, Department of Medicine, UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, CA.

The cardiac autonomic nervous system consists of 2 branches—the sympathetic and the parasympathetic systems—that work in a delicately tuned, yet opposing fashion in the heart. This extrinsic control mechanism can dominate intrinsic regulatory mechanisms that modulate heart rate and cardiac output. These branches differ in their neurotransmitters (norepinephrine and acetylcholine) and exert stimulatory or inhibitory effects on target tissue via adrenergic and muscarinic receptors. Stimulation of the sympathetic branch exerts facilitatory effects on function, increasing heart rate and myocardial contractility, whereas the stimulation of the parasympathetic branch exerts inhibitory effects that decrease heart rate and contractility. The interplay between these two branches is complex and susceptible to control at several levels, from centrally mediated baroreceptors and chemoreceptors to local interneuronal interactions.

Alterations in autonomic function occur in several interrelated cardiac conditions including sudden cardiac death, congestive heart failure, diabetic neuropathy, and myocardial ischemia. Although the full extent of these changes has not been elucidated, multiple autonomic remodeling mechanisms have been observed at both the neuronal fiber and myocardial cellular level that contribute to an arrhythmogenic substrate. We describe the anatomy of both systems in this review. However, the review will premdominantly focus on the sympathetic system, whose role in the modulation of cardiac arrhythmias is slightly better delineated.

Cardiac Autonomic Innervation: Neuroanatomy

Both branches of the autonomic nervous system are composed of both afferent and efferent as well interneuronal fibers (Fig 1). Sympathetic innervation originates mainly in the right and left stellate ganglia. These fibers travel along the epicardial vascular structures of the heart and penetrate into the underlying myocardium similar to coronary vessels and end as sympathetic nerve terminals reaching the endocardium. Based on norepinephrine content studies, a gradient exists in sympathetic innervation from atria to the ventricles and from base to apex of the heart. Therefore, the atria are most densely innervated, but the ventricles are also supplied with a sympathetic network, most densely at the base.[1]

Parasympathetic effects are carried by the right and left vagus nerves, originating in the medulla. The vagus nerve further divides into the superior and inferior cardiac nerves, finally merging with the postganglionic sympathetic neurons to form a plexus of nerves at the base of the heart, known as the cardiac plexus. In contrast to sympathetic neurons, after parasympathetic fibers cross the atrioventricular (AV) groove along the surface of the heart,

Address reprint request to Kalyanam Shivkumar, MD, PhD, UCLA Cardiac Arrhythmia Center, Division of Cardiology, Department of Medicine, 47-123 CHS, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles CA 90095-1679. E-mail: kshivkumar@mednet.ucla.edu.

they plunge across the ventricular wall into subendocardium before projecting their individual terminal axons intramurally.[2] Parasympathetic neurons are distributed much more heterogeneously throughout the heart than sympathetic neurons. The density of parasympathetic innervation in the sino-atrial (SA) and AV nodes is considerably higher than the surrounding atrial or ventricular tissue. Ventricular parasympathetic innervation is sparse, whereas atrial parasympathetic fibers lie in fat pads, predominantly in the superior and posterior aspects of the atria.

Effects of the Sympathetic Nervous System on the Normal Myocardium: Activity and Signaling Mechanisms

The major neurotransmitter mediating sympathetic response is norepinephrine; of note, epinephrine release during activation is negligible (Fig 2).[3] Along the length of terminal axons are a series of localized swellings known as "varicosities," around 1 to 3 μm and up to 4 μm in length. Most of the norepinephrine storage vesicles in a terminal axon are concentrated in these varicosities. Each individual varicosity acts as a specialized site of norepinephrine storage and release.[4]

The source of biosynthesis of norepinephrine is the amino acid tyrosine, which is converted enzymatically to dihydroxyphenylalanine and then to dopamine. Dopamine is then transported into storage vesicles by active transport and transformed to norepinephrine by vesicular enzyme B hydroxylase. Neuronal stimulation leads to norepinephrine release through fusion of vesicles with the neuronal membrane. Apart from neuronal stimulation, release is also regulated by presynaptic receptor systems, including α2 adrenergic receptors, which provide a negative feedback on exocytosis.[5]

α2 Adrenergic receptors have also been found in the postsynaptic canine Purkinje fibers of the myocardium (although not in the muscular fibers). Stimulation of these α2 adrenergic receptors prolongs action potential duration and suppresses β-adrenergic stimulation–induced delayed afterdepolarization.[6,7]This has further been shown to protect against ischemia induced ventricular tachycardia in vivo,[8] and α2 adrenergic receptor antagonism enhances the risk of ventricular tachycardia in ischemia.[9]

Increased sympathetic stimulation increases discharge of the SA node and augments AV nodal conduction, leading to an increase in heart rate. In atrial and ventricular myocardium, contractility is also increased. Increased contractility is mediated by postsynaptic myocardial β-adrenergic receptors. These receptors are highly abundant in myocardium and exert choronotropic, dromotropic, and inotropic effects. Both β1 and β2 subtypes are present with a ratio of approximately 5:1 in the healthy human heart.[10–12] α Adrenoreceptors are mainly present in the vascular wall but are also found in ventricular myocardium, where they account for approximately 15% of cardiac adrenergic receptors.[12]

In 1989, a third cardiac β-adrenergic receptor, β3, was described, and its gene was cloned. Interestingly, in full contrast to the other 2 β-adrenergic subtypes, stimulation of this receptor results in a decrease in cardiac contractility and vasodilation, likely through the nitric oxide synthase pathway.[13–15] Furthermore, β3 receptors are stimulated by catecholamines only at high doses.[14] The observed increase in chronotropic response after β3 receptor stimulation is thought to be from baroreceptor-mediated withdrawal of vagal input due to sodilation.[15] For the purposes of the following review, we will focus on the β1-and β2-adrenergic receptors, as their roles in normal and diseased myocardium is better elucidated.

Norepinephrine binds postsynaptically to myocardial β-adrenergic receptors, which are linked intracellularly to the enzyme adenylate cyclase by the stimulatory guanine nucleotide binding

protein Gs. Stimulation of adenylate cyclase increases intracellular levels of second messenger cyclic adenosine monophosphate (cAMP). Elevated cAMP levels activate protein kinase A (PKA), which phosphorylates L-type calcium channels, leading to an influx of Ca^+ into myocytes. This influx releases stores of intracellular Ca^+ from the sarcoplasmic reticulum, further increasing the amount of Ca^+ available for activation of myocardial contractions through the Ca-calmodulin–regulated formation of myofilament cross-bridges. This and other intracellular signaling mechanisms lead to the enhanced myocardial contractility. Finally, norephinephrine has been shown to stimulate several other ventricular currents, including inward sodium current, the delayed rectifier potassium current, I_{Ks}, the chloride current, and the pacemaker current. The overall effect in humans is shortening of ventricular action potential duration (APD) and refractory period.[16]

The effect of β receptor stimulation of the delayed rectifier potassium current, I_{Ks}, is notable. Genetic mutations in the α (KCNQ1) and β (KCNE1) subunits of I_{Ks} underlie long QT syndromes, LQT1 and LQT5, and predispose carriers to polymorphic ventricular tachycardia (VT) in the face of increased sympathetic stimulation. Protein kinase A regulation of the channel is coordinated by a macromolecular signaling complex composed of the channel and the targeting protein Yotiao, which recruits PKA and protein phosphatase 1 to the carobxy terminal domain of KCNQ1 subunit.[17] This complex forms a channel that permits sensitive temporal control of the channel's phosphorylation state in response to sympathetic activation. Protein kinase A phosphorylation of I_{Ks} results in an increase in the rate of activation of the channel and a reduction in the channel deactivation rate, leading to potassium efflux and APD shortening. Furthermore, as heart rate increases and APD becomes shorter, there is incomplete deactivation of I_{Ks} between beats, resulting in accumulation of channels in the open state during diastole. Although there is no current flow during diastole because of the lack of a driving force, the open channels conduct during the next action potential upstroke. As a result, channels that buildup in the open state are deactivated slower, and I_{Ks} becomes larger with successive increases in heart rate, which causes further APD shortening in the face of β-adrenergic stimulation.[18] In some patients with LQT1 and LQT5, sympathetic regulation of I_{Ks} is disrupted. Models of I_{Ks} kinetics predict that this could lead to decreased I_{Ks} deactivation and reduced APD adaptation at faster heart rates. Cardiomyocytes cannot fully repolarize between beats, and a window of cycle length for which APD alternans occurs can be predicted.[18]

In the synaptic cleft, only a small amount of released norepinephrine is available to activate β receptors. Most norepinephrine undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter and recycles into vesicles or is metabolized in the cytosol by monoamine oxidase. A small fraction diffuses into the vascular space where it can be measured in coronary sinus blood. Norepinehprine spillover can be measured and used to infer sympathetic outflow to the heart and can also be assessed in humans.[19]

Not all channels are distributed homogenously in the different layers of the myocardium. For example, the density of sodium-calcium exchanger is highest in the epicardium and lowest in the endocardium, and this transmural heterogeneity can be disrupted in heart failure.[20] Transmural dispersion of ventricular repolarization has been demonstrated in intact canine ventricles. At baseline, APD is shortest in the epicardium and endocardium and longest in the mid myocardium. During sympathetic stimulation in the normal ventricle, this transmural dispersion of repolarization is decreased, so that sympathetic stimulation decreases APD of midmyocardial myocytes more than epicardium or endocardium, reducing this dispersion of repolarization. Interestingly, sympathetic stimulation can produce early afterdepolarization in these experiments.[21]

Effects of the Parasympathetic Nervous System on the Normal Myocardium: Activity and Signaling Mechanisms

Acetylcholine, the transmitter of the parasympathetic system, is synthesized by transport of choline into the cytosol of the nerve terminal through high-affinity choline transporter and acetylation by choline acetyl transferase.[22,23] Acetylcholine is stored in vesicles and is released by parasympathetic stimulation, activating primarily postsynaptic muscarinic and preganglionic nicotinic receptors.[24,25] The effects are terminated by rapid degradation by acetylcholinerases.[26]

Increased parasympathetic stimulation decreases heart rate by decreasing SA node discharge rate and AV node conduction velocity. Ventricular contractility is not affected by parasympathetic activity when background sympathetic discharge is low but is enhanced in the presence of sympathetic activation.

In ventricular myocardium, the primary postsynaptic receptor of acetylcholine is the type M2 muscarinic receptor, which is linked to adenylate cyclase by the inhibitory guanine nucleotide binding protein Gi. Activation of this receptor by acetylcholine decreases intracellular cAMP production, thereby reducing contractility. In atrial and nodal tissue, M2 receptors activate another G protein, Gk, which causes an increase in K efflux by directly inducing K channel opening, independent of second messenger systems. Given the lack of multiple intracellular messenger systems with parasympatheic as compared with sympathetic activation, the heart responds more quickly to stimulation by the parasympathetic branch, and the influence of parasympathetic system can also cease much more rapidly. This, in particular, is because unlike norepinephrine, which is highly conserved and is taken up by neurons after release, acetylcholine is rapidly hydrolyzed by acetylcholinesterase. No acetylcholine transporter exists, and only choline is taken back up into the neuron to be resynthesized into new acetylcholine molecules.[27]

Unlike the sympathetic nervous system, parasympathetic stimulation does not affect action potential duration and transmural dispersion in the endocardium, epicardium, or mid myocardium.[21]

The Cardiac Nervous System

Data collected over the past 3 decades indicate that the intrinsic cardiac nervous system, including the intrinsic cardiac ganglia, are not simply “relay stations” of parasympathetic or sympathetic efferent input to the heart. Extensive amounts of processing occur in the intrinsic cardiac nervous system that forms a plexus at the base of heart, involving the afferent neurons, interconnecting interneurons and local circuits, as well as both sympathetic and parasympathetic efferent postganglionic neurons. Intrinsic cardiac ganglia and interneurons process information from the sympathetic and parasympathetic system as well as myocardial sensory neurons and also send projections to other cardiac ganglia.[28] Furthermore, the plexus at the base is composed of 7 ganglionic subplexuses, containing more than 800 epicardial ganglia in total. Each subplexus or group of subplexuses innervate different chambers of the heart. One subplexus innervates the right ventricle, 3 innervate the left ventricle, whereas the remaining innervate the atria. The highest density of epicardial ganglia, approximately 50%, exists near the hilum of the heart, especially on the dorsal and dorsolateral surfaces of the left atrium. Interestingly, the number of ganglia decreases with age. Approximately 43000 intrinsic neurons maybe present in the epicardial neural plexus of the adult heart, whereas 94000 neurons innervate young hearts, including fetuses, neonates, and children.[29] A complex feedback regulatory system allows the cardiac nervous system to modulate the amount of sympathetic and parasympathetic input to the heart.

Myocardial Infarction, Heart Failure, and Sympathetic Innervation

It has been known for decades that sympathetic activation can trigger malignant arrhythmias, whereas vagal activity may exert a protective effect (Fig 3 and Fig 4). Transmural myocardial infarction (MI) causes denervation and death of sympathetic fibers within the scar. Areas of dense scar do not respond to either sympathetic nerve stimulation or norepinephrine infusion. In the early 1980s, in a canine model of MI, sites apical (distal) to the infarct were shown to demonstrate an abnormal response to sympathetic stimulation. Although noninfarcted sites proximal to the infarct showed effective refractory period (ERP) shortening with both sympathetic (stellate ganglia) stimulation and norepinephrine infusion, sites within noninfarcted myocardial sites distal (apical) to the infarction did not show homogenous ERP shortening with sympathetic nerve stimulation. [30] Yet, most of these noninfarcted sites showed ERP shortening with norepinephrine infusion, and a few showed ERP shortening with stimulation of either the left or the right stellate ganglion, but not both.[30] Furthermore, these noninfarcted areas showed denervation super-sensitivity, defined as an exaggerated shortening of ERP to both norepinephrine and isoproterenol infusions, compared with normal myocardium basal to the infarct. Interestingly, the cellular mechanisms for this exaggerated response did not involve detectable differences in β-adrenergic receptor density or α subunit of the stimulatory G protein density or affinity in the apical vs basal areas.[31–33] Myocardial infarction produced loss of efferent sympathetic innervation in noninfarcted apical sites as early as 5 to 20 minutes after coronary occlusion, with more significant loss occurring over the following 3 hours.[33] Hence, disruption of neurotransmission, likely due disruption of sympathetic fibers that run along the coronaries, can lead to a heterogenous response in ERP even in areas of viable noninfarcted myocardium situated apical to the infarct. Furthermore, the innervation of these areas is also heterogenous because not all sites appeared to be sympathetically denervated. The denervated sites, although no longer responsive to nerve stimulation, demonstrated denervation supersensitivity to infusion of β agonists. Interestingly, they show evidence of norepinephrine depletion on histologic and histofluorescent catecholamine analysis, although they appear to be histologically normal. These studies were confirmed by Yoshioka et al[34] in rabbits with regional denervation due to application of phenol. Activation recovery interval (ARI), a surrogate of ERP, was used in these studies to show that norepinephrine infusion shortened ARI in 98% of denervated regions, with increase in both shortening and dispersion of ARI in more severely denervated regions. On the other hand, left stellate ganglion stimulation shortened ARI in only 30% of denervated areas with similar increase in dispersion seen in more severely denervated areas. Surprisingly, left stellate ganglion stimulation prolonged ARI in the other 70% of denervated areas, with no correlation to severity of denervation. The importance of these studies were in demonstrating that transmural MI cannot only alter the substrate for ventricular arrhythmias by creating a scar but can disrupt innervation to histologically normal myocardium distal to the infarct, leading to a nonuniform electrophysiologic response early in the stages of acute ischemia. The heterogenous response to left or right sympathetic nerve stimulation, an exaggerated response to circulating catecholamines, and reduced protection from vagal denervation all contribute to the genesis of ventricular arrhythmias in both acute and chronic MI.

Further insight into the mechanistic basis of noradrenergic nerve terminal abnormalities in heart failure was gained from rapid ventricular pacing induced heart failure models of dogs. A diffuse decrease in myocardial norepinephrine content and elevated blood norepinephrine levels were observed in failing ventricles. This was also likely due to loss of noradrenergic nerve terminals similar to MI models as evidenced by a reduction in catecholaminergic histofluorescence and tyrosine hydroxylase immunostained profiles.[35] Interestingly, similar reduction abnormalities could be produced in normal dogs subjected to 8 weeks of chronic norepinephrine infusion, even without elevated filling pressures, providing evidence that chronically elevated levels of norephinephrine, which is often seen in humans with heart

failure, could lead to cardiac noradrenergic nerve abnormalities similar to those found in failing myocardium.

As with heart failure, abnormal sympathetic innervation has also been observed in diabetic patients using C-11 hydroxyephedrine, a norepinephrine analog, and positron emission, with maximal denervation affecting distal myocardial segments. Patients with poor glycemic control have a more heterogenous hydroxyephedrine uptake, with increased retention in the proximal myocardial segments and much more extensive decrease in retention in distal segments.[36]

Following studies showing acute denervation due to MI and heart failure, evidence of nerve sprouting and heterogenous hyperinnervation was shown in chronic infarction and heart failure models. MIBG studies had shown both sympathetic denervation and reinnervation in injured myocardium in both ischemic and nonischemic cardiomyopathy in humans.[37,38] A consequence of peripheral nerve injury resulting in Wallerian degeneration is regeneration via nerve sprouting. The axonal regeneration is slow but accelerates to reach a constant rate by third day after injury and is triggered by NGF produced by surrounding myocardium.[39,40] Excessive and uncontrolled regeneration could lead to hyperinnervation of the myocardium. Vracho et al[41,42] demonstrated abnormal patterns of neurilemma proliferation in the scars of human myocardium. These studies were confirmed by Cao et al[43] who showed local increases in sympathetic nerves in the periphery of necrotic tissues and in perivascular regions of the hearts of 53 patients with heart failure who underwent cardiac transplantation by using immunochemical staining for S-100 protein, neurofilament protein, and tyrosine hydroxylase on explanted hearts. These changes were scattered in a “swarmlike” pattern at the junction between necrotic and surviving myocardium and were significantly higher in patients with history of ventricular arrhythmias than those without. These borderzones of infarcts have been shown to be frequent sites of origin of inducible ventricular tachycardia and ventricular fibrillation (VF) 1 week after left anterior descending artery (LAD) occlusion in dogs.[44,45] Multiple areas of regional denervation were seen in areas of necrosis or fibrosis in the explanted human hearts, as previously reported (Fig 3).[43]

The role of NGF in promoting nerve sprouting has also been studied in animal models of infarction. NGF infusion to the left stellate ganglion results in nerve sprouting in normal dogs. In infarct models of dogs caused by LAD ligation and complete AV block created to induce remodeling, greater sympathetic nerve sprouting occurs with NGF infusion into the left stellate ganglion compared with dogs without an NGF infusion pump. Furthermore, although all dogs show spontaneous VT after MI, spontaneous VT reappeared approximately 2 weeks later in the group with the NGF infusion with higher frequency and showed a diurnal variation, with peak incidence in the morning to early afternoon. Sudden cardiac death due to ventricular fibrillation appeared only in the NGF infusion group. However, even dogs without NGF infusion or AV block had evidence of nerve sprouting by 50 days post infarction. Therefore, NGF infusion accelerates and intensifies the magnitude of nerve sprouting, resulting in higher incidence of sudden cardiac death. Furthermore, NGF infusion to the left stellate ganglion resulted in nerve sprouting in normal dogs but did not cause ventricular arrhythmias or SCD.[46] A differential response of QTc and ventricular arrhythmia was seen when the left vs the right stellate ganglia were infused with NGF. Infusion into the left stellate ganglion cause sympathetic nerve sprouting on immunocytochemical staining in the left ventricle, with resulting QTc prolongation and sudden cardiac death in 50% of the experimental dogs. Right stellate ganglion NGF infusion, on other hand, results in right ventricular nerve sprouting, shortened QTc interval, and no sudden cardiac death.[47]

The mechanism of cardiac nerve sprouting due to NGF has been studied in dog models of MI. Transcardiac NGF increased immediately after MI, whereas expression of NGF and growth associated protein 43 was increased within 3.5 hours after MI. These changes were more

pronounced at the infarcted than noninfarcted sites, 4-fold higher than the noninfarcted control group. However, cardiac nerve sprouting and sympathetic hyperinnervation were more pronounced at the noninfarcted than infarction sites, peaking 1week after MI. Persistent elevation of NGF levels in the aorta and the coronary sinus were seen 1 month after MI. Furthermore, NGF and GAP 3 levels increased in the left stellate ganglion of these dogs 3 days after MI, without a concomitant increase in mRNA, indicating possible retrograde transportation of these proteins to the left stellate ganglion, which then triggers nerve sprouting in noninfarcted left ventricular sites.[48]

Further evidence that sympathetic nerve sprouting is arrhythmogenic stems from studies of hypercholesterolemic rabbits compared with normal controls. Rabbits fed a high-cholesterol diet for 8 weeks had significantly higher densities of growth-associated protein 43 (a protein associated with axonal growth cone) and tyrosine hydroxylase, indicating nerve sprouting and sympathetic hyperinnervation. They also showed longer QTc intervals, more QTc dispersion, longer action potential duration, increased heterogeneity of repolarization, and higher peak calcium current density. Furthermore, significantly higher episodes of ventricular fibrillation, both spontaneous and induced, occurred in the hypercholesterolemic rabbits, indicating a lower vulnerability to fibrillation.[49] Cardiac nerve sprouting appears to be highly plastic and has been has been shown in other models of heart failure including rapid pacing where dogs with the most hyperinnervation have the highest risk of sudden cardiac death,[50] in stem cell transplantation,[51] and radiofrequency ablation.[52]

Heart failure is also known to cause spatially heterogenous remodeling of cardiomyocytes, with further remodeling of cardiac ion channels, including Ca, K, Cl, and Ca transporters and enzymes in the border zones surrounding the infarct. Specifically, an increase in L-type Ca current density and decrease in potassium current densities are observed in heart failure.[53–55] I_{Ks} and I_{Kr} are also responsible for the increased sudden cardiac death seen in LQT1 and LQT2. Furthermore, epinephrine may induce torsade, whereas left sympathectomy and β-blockers are antiarrhythmic in LQT1.[56,57] These studies suggest that sympathetic activation is arrhythmogenic if I_{Ks} is abnormal or down-regulated. Furthermore, over-expression of NGF in adult transgenic mice results in further decrease in density of at least 2 other potassium currents, I_{to} and I_{Kur}.[58] Thus, in areas of hyperinnervation with higher concentration of norepinephrine and neuropeptide Y, sympathetic stimulation could result in prolongation, instead of shortening of action potential duration, accentuating preexisting heterogeneity of excitability and refractoriness and contributing to arrhythmia susceptibility. Furthermore, superimposed upon prolongation of action potential duration and increased I_{CaL} density, sympathetic stimulation can lead to intracellular Ca overload induced triggered activity, potentiating the risk spontaneous ventricular arrhythmias. Therefore, an interaction between areas of denervation, regional nerve sprouting (neural remodeling) in the left ventricle, and electrical remodeling due to heart failure all combine to create a high-yield substrate for ventricular tachycardia, fibrillation, and sudden cardiac death (Fig 4).

Effect of Sympathetic Stimulation on Action Potential Duration Restitution

Substantial evidence links enhanced sympathetic activation with ventricular arrhythmias and sudden cardiac death.[59–61] Destabilization of ventricular wave fronts leading to degeneration ventricular tachycardia into ventricular fibrillation appears to be related to the restitution properties of action potential duration.[61,62] Restitution is described as the change in APD in response to the preceding diastolic interval, and steeply sloped restitution curves with large changes in APD for relatively small changes in diastolic interval over a wide range of diastolic intervals have been associated with complex unstable dynamic rhythms.[62,63] Sympathetic stimulation with epinephrine in porcine models increases the slope of ventricular APD restitution curves.[64] This was confirmed in humans in whom stimulation with both adrenalin

and isoproterenol increased the steepness of the slope of APD restitution curves, further demonstrating the known effects of adrenergic stimulation in facilitating ventricular fibrillation.[65]

Cardiac Parasympathetic Nervous System Dysfunction as Manifested by Baroreflex Sensitivity and Heart Rate Variability

As mentioned earlier, the loss of protective vagal reflexes is associated with ventricular tachycarrhythmias in heart failure and MI. Depressed baroreflex sensitivity (BRS) and heart rate variability (HRV), reflections of parasympathetic innervations, have been associated in humans and animal models of MI with a greater susceptibility to ventricular fibrillation during and after ischemic episodes.[66] Heart rate variability primarily reflects tonic vagal activity, whereas BRS measures predominantly reflex vagal activity in response to stressors. Middle-aged healthy men with high resting heart rates (>75 beats per minute) had a 3.8-fold increase in the risk of SCD compared with those with low basal heart rates (<60 beats per minute), with the risk of SCD increasing linearly with increasing resting heart rates over 23 years of follow-up, suggesting that high parasympathetic tone is protective against SCD.[66]

Heart Rate Variability

Beat to beat, heart rate is not completely regular and is based in part on the autonomic innervation of the sinus node. This can serve as noninvasive marker of autonomic input to the heart, and the analysis can be accomplished in time or frequency domains. High frequencies are thought to be represent the parasympathetic component of the autonomic nervous system, whereas low frequencies are mediated by both the sympathetic and parasympathetic nervous system and are affected by BRS. Very low frequencies are influenced by many factors including the renin-angiotensin system and thermoregulation.[67]This measurement is limited by its inherent use of sinus node innervation as a surrogate for ventricular parasympathetic innervation.

In dog models of MI, Hull et al[68] showed that dogs who developed ventricular fibrillation had a significant decrease in all measures of HRV, demonstrating a high sensitivity and specificity of HRV in predicting susceptibility to ventricular arrhythmias. These studies were further confirmed by Adamson et al[69] who also showed that low-risk dogs recovered HRV after MI, whereas high-risk dogs continued to have depressed HRV parameters. Similar results were obtained in humans. Twenty-four-hour Holter recordings in post-MI patients showed that depressed HRV was a significant predictor of mortality after adjusting for clinical and demographic features, including ejection fraction (EF). These studies were further confirmed by other in post-MI patients, showing that impaired HRV was an independent predictor of cardiac mortality only within 6 months of MI and seemed to improve over time.[70,71] That HRV improves over time is consistent with the decreasing risk of SCD after MI over a similar period. One of the largest of these trials involved 808 patients who underwent HRV analysis using 24-hour Holter monitors 11 ± 3 days post acute MI. In univariate analysis, HRV below 50 milliseconds imposed a hazard relative risk of 5.3, compared with patients with HRV above 100 milliseconds and remained a significant predictor of mortality after adjusting for clinical and demographic characteristics, other Holter features, and ejection fraction during a mean follow-up of 31 months.[72] Of note, decreased HRV parameters have also been reported in patients with idiopathic dilated cardiomyopathy with history of sudden cardiac death compared with those without a history of ventricular tachyarrhythmias.[73]

Baroreflex Sensitivity

The arterial baroreceptor control of heart is generally studied using 3 techniques: (1) increasing blood pressure with vasoconstrictors such as phenylephrine and analyzing heart rate response —this method is used most commonly; (2) lowering blood pressure with vasodilators such as nitroprusside to test reflex sympathetic tone; (3) direct stimulation of carotid baroreceptors with neck suction.[67] Just as in HRV, BRS was shown to be reduced after MI and to predispose to ventricular fibrillation first in dog MI models.[66] These studies were carried forward to humans, where BRS was found to be lower in patients after MI than in control subjects, but the reduction was transient and appeared to return to baseline levels within 3 months, similar to the improvement seen in HRV and decreasing risk of SCD.[74] The potential prognostic value of BRS was established in several human studies showing that a severely depressed BRS (<3 milliseconds/mm Hg) was associated with high mortality due to a high risk of arrhythmic events. The largest of these was the Autonomic Tone and Reflexes After Myocardial Infarction (ATRMI) study, a multicenter prospective trial of 1028 patients who underwent HRV and BRS analysis within 1 month after MI. During 21 months of follow-up, low values of either heart rate variability (SDNN <70 milliseconds) or BRS (<3.0 milliseconds/mm Hg) carried a significant multivariate risk of cardiac mortality (3.2 [95% CI, 1.42–7.36] and 2.8 [95% CI, 1.24–6.16], respectively). The association of low standard deviation of normal RR intervals (SDNN) and BRS further increased risk with the 2-year mortality being 17% when both were low and 2% when both were well preserved (SDNN >105 milliseconds, BRS >6.1 milliseconds/mm Hg).[75] In patients with EF above 35% after MI, depressed BRS (<3.0 milliseconds/mm Hg) has identified, independently of age and EF, a subgroup of patients at long-term high risk of cardiovascular mortality (HR, 11.4 [95% CI, 3.3–39]) who may benefit from more aggressive preventive strategies.[76] Of note, BRS is improved in patients with MI who receive thrombolytic therapy or revascularization compared with those treated conservatively.[77]

Parasympathetic Modulation of Sudden Death: BRS vs HRV

Although both HRV and BRS have been shown to be abnormal in heart failure and in post-MI patients, the correlation between the two is only moderate ($R = 0.63$).[78], This is consistent with the fact that HRV and BRS are different measures of parasympathetic activity, with HRV measuring tonic vagal activity over a 24-hour period, whereas BRS is equivalent to a vagal response or variability stress test. Furthermore, BRS in some studies has been a stronger predictor of ventricular tachyarrhythmias than HRV, suggesting that measurements of the dynamic nature of the parasympathetic system may provide superior prognostic information.[79]

The underlying mechanisms of the protective effects of the parasympathetic nervous system are not well understood. Loss of vagal innervation, similar to sympathetic innervation, occurs as early as 5 to 20 minutes after coronary occlusion.[33] Vigorous vagal activation during acute myocardial ischemia has been shown to be protective against ventricular fibrillation in anesthetized cats. Vagal stimulation in these animals after coronary artery ligation increases ventricular repolarization by increasing levels of pertussis toxin–sensitive G protein and reduces the risk of ventricular fibrillation. This reduction in risk is no longer observed if vagal stimulation is blocked by atropine or pertussis toxin.[80] The antifibrillatory effects of vagal activation is confirmed by the prevention of ventricular fibrillation during acute ischemia in dogs susceptible to sudden cardiac death by direct stimulation of the right vagus.[81]

In animal studies, direct muscarinic and vagal nerve stimulation with carbacholine, cyclic guanine monophospate (cGMP), noestigmine, or oxgremorine or even indirect increase with exercise have been shown to reduce the incidence of ventricular tachyarrhythmias in dog infarct models of sudden cardiac death.[82–87] Based on these studies, low-dose scopolamine was used

in humans and was shown to increase HRV and BRS in healthy and in post-MI patients.[88] Endurance exercise training in healthy human subjects also leads to an increase HRV in healthy subjects, suggesting increases in vagal tone.[87] Whether these changes translate into improved mortality and decreased risk of ventricular arrhythmias remains unclear. Post–MI dogs treated with low-dose scopolamine compared with controls continued to have a high risk of sudden cardiac death and recurrent ventricular fibrillation despite improvement in HRV parameters.[89] Thus, interventions that improve vagal tone may not provide antifibrillatory effects, and those that improve reflex tone may prove to be better targets for reducing the risk of ventricular arrhythmias. Until the cellular mechanisms of the protective effects of vagal innervation are understood, targeting the parasympathetic nervous system in ischemic cardiomyopathy and prevention of sudden cardiac death will prove difficult.

Therapies That Reduce Sudden Cardiac Death Modulate Neurohormonal Remodeling

As sympathetic tone is known to be increased and parasympathetic innervation decreased in cardiomyopathy patients, interventions that aimto reduce sympathetic tone and, therefore, increase parasympathetic tone, should reduce the risk of sudden cardiac death and ventricular tachyarrhythmias (Fig 5). This, has in fact, been shown to be true.

Selective Sympathetic Blockade

In 1983, Schwartz et al[90] showed that the incidence of ventricular fibrillation was decreased from 66% to zero by performing left stellectomy in post-MI dogs. Issa et al[91] demonstrated that thoracic spinal cord stimulation at T1–T2 segments reduced the incidence of ventricular tachyarrhythmias in canine model of ischemic cardiomyopathy from 59% to 23% when applied during myocardial ischemia. Furthermore, they observed a simultaneous decrease in heart rate and reduced systolic blood pressure, consistent with the antisympathetic effects of spinal cord stimulation.[92–95] In a similar model, intrathecal clonidine, which is known to cause centrally mediated bradycardia and hypotension because of its sympatholytic effects, when delivered via a catheter at T2–T4 spinal segments, also significantly reduced the occurrence of ventricular tachycardia and fibrillation during transient myocardial ischemia.[96]

The report of sympathetic blockade in humans compared survival in a group of 49 patients with recurrent ventricular fibrillation (electrical storm) early after MI treated with standard advanced cardiac life support (ACLS) protocol vs sympathetic blockade.[97] Sympathetic blockade was established using left stellate ganglionic blockade in 6 patients and infusions of either propranolol or esmolol in 21 patients without antiarrhythmic therapy as recommended by ACLS. The 1-week and 1-year mortality were significantly higher in the group undergoing standard ACLS protocol, compared with the sympathetic blockade group (82% vs 22% at 1 week, 95% vs 33% at 1 year, respectively).[97] Successful treatment of recurrent ventricular tachycardia, refractory to antiarrhythmic therapy, can be achieved by neuraxial modulation at the level of the spinal cord. The benefit of thoracic epicardial anesthesia was reported in a patient with ischemic cardiomyopathy and recurrent ventricular arrhythmia refractory to intubation and sedation, with the use of 0.25% Bupicavaine at T1–T2 interspace, reducing the number of ICD shocks from 86 in 48 hours to zero.[98]

Medical Therapies Modulating Cardiac Autonomics

As mentioned above, β-blockers, but also angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers, aldosterone antagonists, statins, and fish oil have been shown to decrease risk of SCD in ischemic cardiomyopathy and significantly improve mortality.[99–106] These classes of drugs have also been shown to modulate the autonomic nervous system to decrease sympathetic tone and/or increase parasympathetic tone.

Angiotensin II in the nucleus solitarii decreases baroreceptor reflex–evoked vagal bradycardia. Microinjection of angiotensin II into the nucleus of the solitary tract in rats significantly attenuates vagal output to the heart. This can be reversed with losartan, suggesting that ACEI and angiotensin receptor blockers may increase parasympathetic output to the heart, decreasing the risk of ventricular tachyarrythmias.[107] In humans, parasympathetic dysfunction, as measured by abnormal response to valsalva maneuver and respiratory sinus arrhythmia, correlates with severity of heart failure. Treatment of nonischemic cardiomyopathy patients with enalapril for 4 weeks reverses these autonomic abnormalities.[108]

In experimental rat models of ischemic cardiomyopathy, rats treated with the spirinolactone derivative, canrenone, had decreased myocardial norepinephrine content (suggesting decreased hyperinnervation) and increased VF threshold. These antisympathetic effects were augmented if the rats also received ramipiril concomitantly.[109]

As with ACEIs and aldosterone antagonists, statins also improve mortality in cardiomyopathy patients. Pliquette et al[110,111] showed that in rabbits with pacing induced heart failure, statin therapy with simvastatin normalizes sympathetic outflow and cardiovascular reflex regulation and showed a beneficial dose-dependent effect on baroreceptor sensitivity. The underlying mechanism for the beneficial effects of statin therapy in modulating the autonomic nervous system was further elucidated by recording renal sympathetic nerve activity and studying the effect of statins on angiotensin II type I gene expression and nicotinamide adenine dinucleotide phospate (NADPH) oxidase activity (a downstream protein activity by angiotensin II receptor activation) in the rostral ventrolateral medulla of rats. Simvastatin therapy significantly reduced angiotensin II–induced pressor and sympathoexcitatory responses, decreased baseline renal sympathetic nerve activity, and increased baroreceptor control of heart rate. Furthermore, simvastatin down-regulated mRNA and protein expression of angiotensin II type I receptor and NADPH oxidase subunits in the medulla of heart failure rabbits.[112] Lee et al[113] once more demonstrated hyperinnervation in rats with MI as shown by an increase in tyrosine hydroxylase and myocardial norepinephrine levels. But they subsequently went on to show that rats treated with pravastatin had lower arrhythmic scores in programed electrical stimulation studies than controls not treated with a statin or treated with a K-channel blocker. Pravastatin seemed to mediate its antiarrhythmic effects by increasing K_{ATP} activity, as blocking of these potassium channels with the K-channel blocker glibenclamide reversed the beneficial effects of pravastatin.

Fish oil has been shown to specifically decrease risk of sudden cardiac death in cardiomyopathy and post-MI patients.[103–105] In elderly nursing home residents, supplementation with 2 g of fish oil significantly improved both high and low frequency components of HRV and SDNN, suggesting that fish oil can decrease sympathetic tone and increase parasympathetic response.[114]

Effect of Resynchronization Therapy on Sympathetic Activity

Biventricular pacing has been shown to result in hemodynamic improvement in patients with depressed ejection fraction and intraventricular conduction delay. In patients with cardiomyopathy, biventricular pacing resulted in decreased sympathetic nerve activity along with improvement in blood pressure compared with intrinsic conduction in patients with left ventricular dysfunction and intraventricular conduction delay.[115] Furthermore, in 50 patients implanted with biventricular pacemakers and randomized to therapy-on (n = 25) vs therapy-off (n = 25), HRV was significantly improved in patients receiving resynchronization therapy despite a lack of difference between mean atrial cycle length. Therefore, improvement in ventricular performance via resynchronization therapy shifts the cardiac autonomic balance toward a more favorable profile of less sympathetic and more parasympathetic activation.[116]

Conclusions

Both the sympathetic and parasympathetic nervous systems are intricately involved in the modulation of cardiac excitability and arrhythmias. Neural remodeling with decrease in parasympathetic input, along with heterogeneous sympathetic denervation followed by hyperinnervation in addition to the observed structural remodeling of the diseased heart, creates the electrophysiologic substrate necessary to initiate and maintain arrhythmias. Only by a better understanding of the cellular and electrophysiologic mechanisms underlying normal innervation and neural remodeling will the prevention of sudden cardiac death become feasible.

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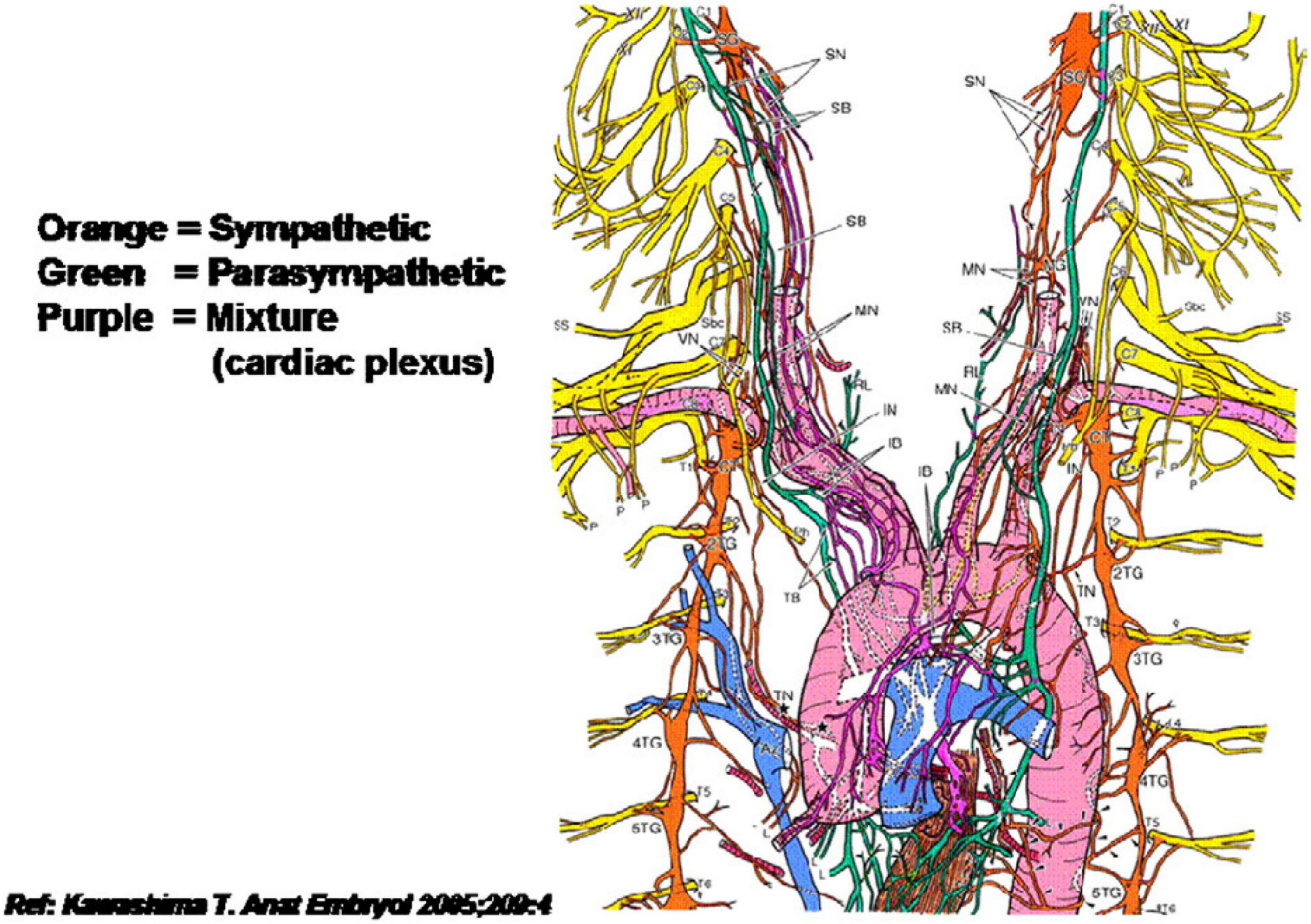

Fig 1.
Neural control of the heart.

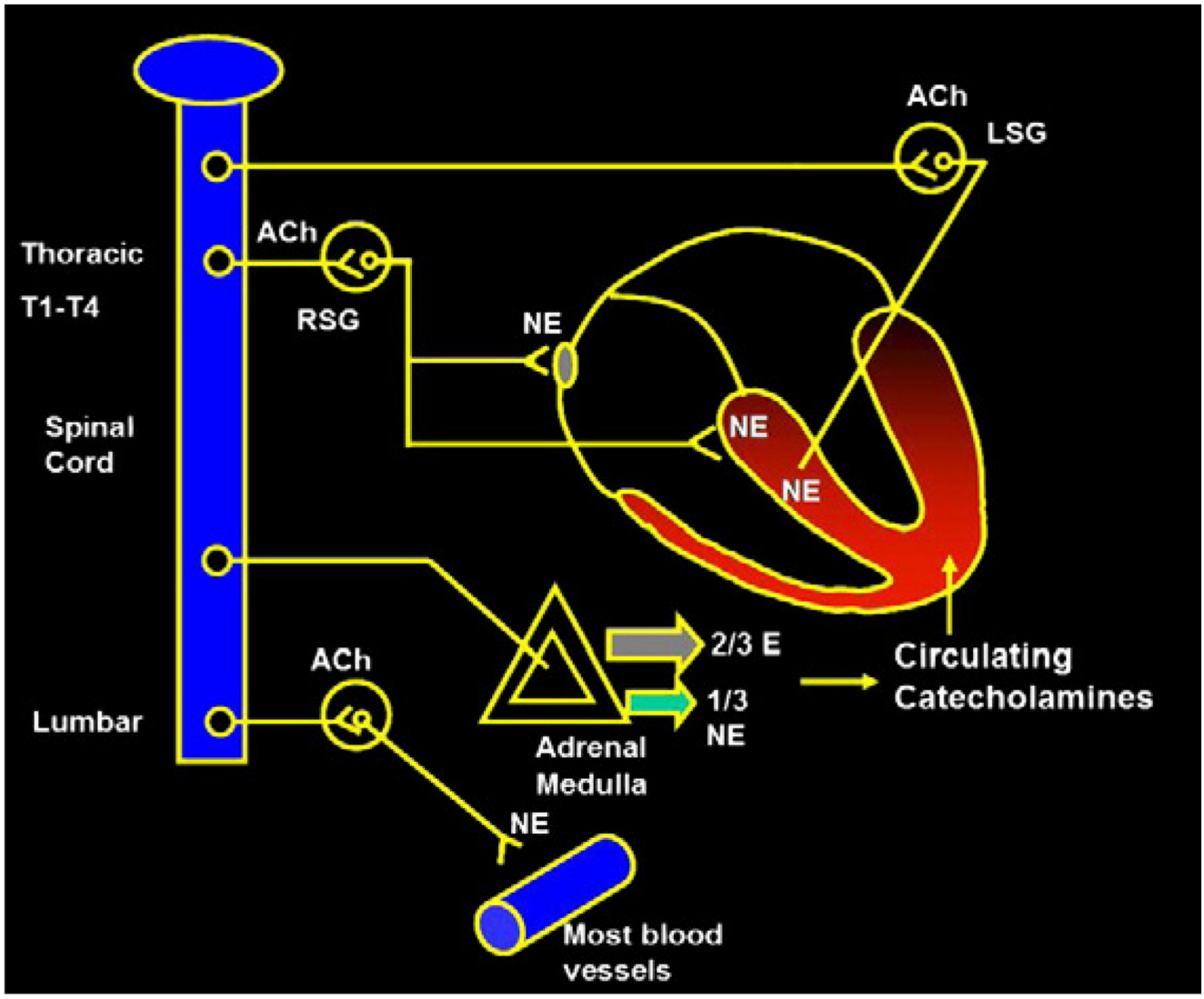

Fig 2.
Cardiac sympathetic control. *Abbreviations*: NE, norepinephrine; Ach, acetylcholine; E, epinephrine.

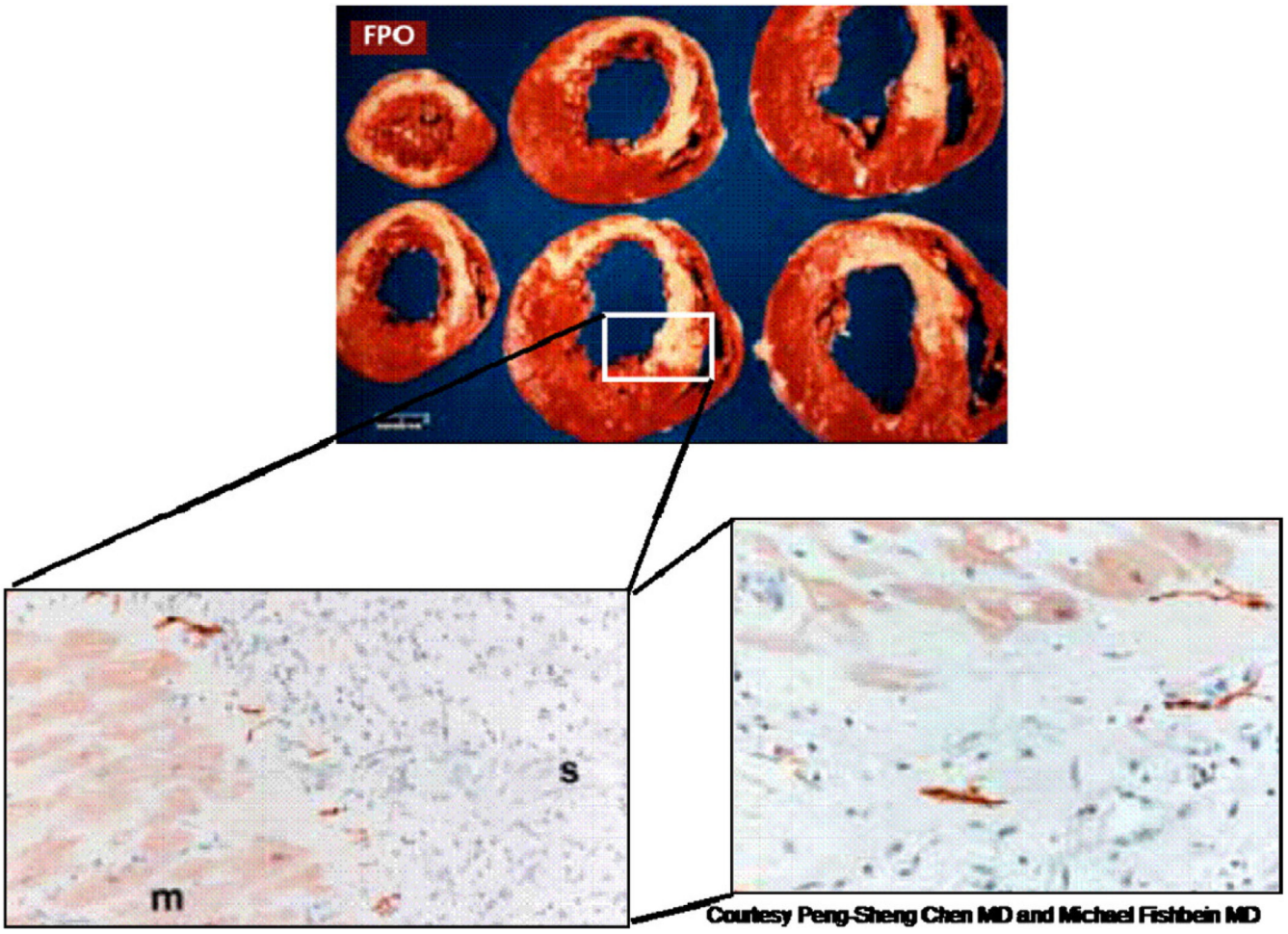

Fig 3.
Neural remodeling and nerve sprouting.

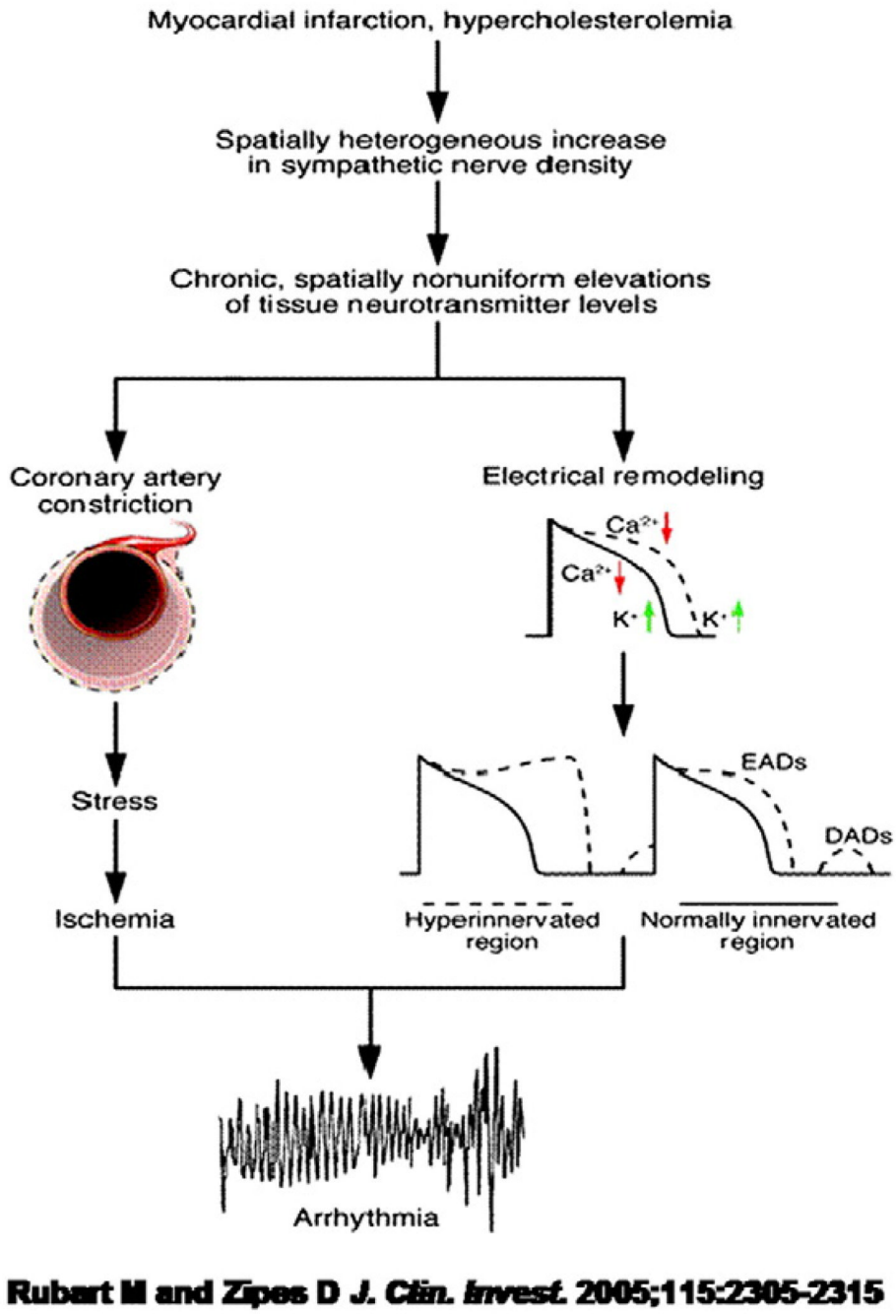

Fig 4.

Factors contributing to arrhythmogenesis in hearts with heterogeneous sympathetic innervation.

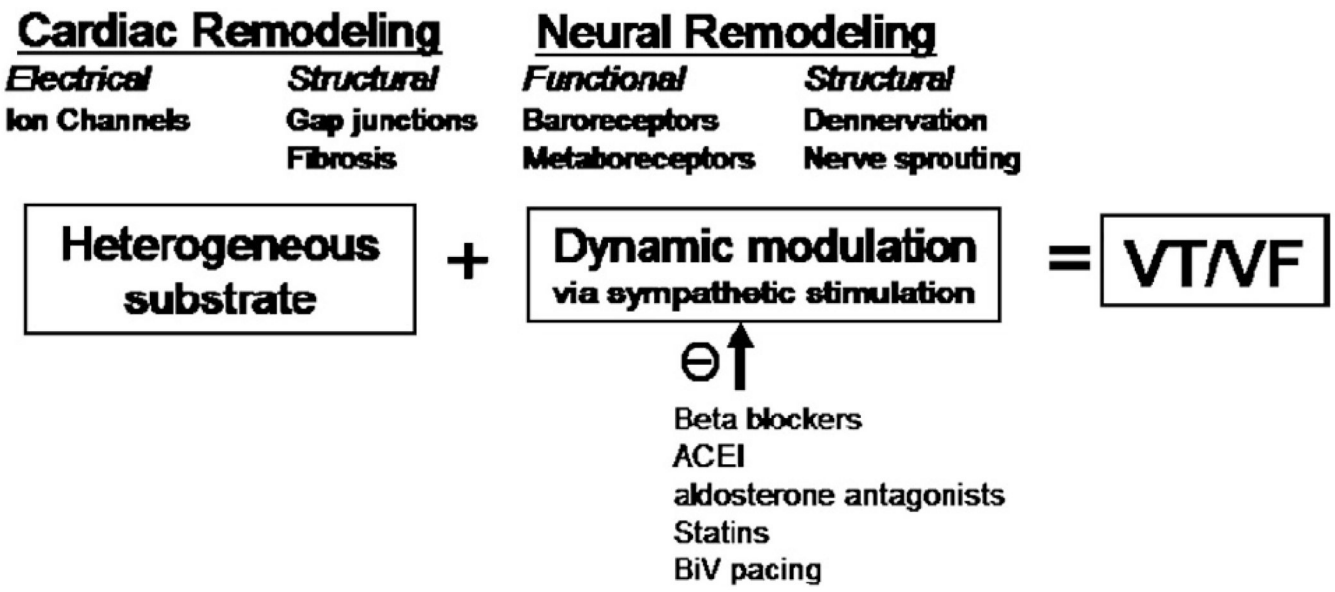

Fig 5.
Structural and functional basis of VT and VF.