Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death

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Abstract

The purpose of this article is to review the nerve sprouting hypothesis of sudden cardiac death. It is known that sympathetic stimulation is important in the generation of sudden cardiac death. For example, there is a diurnal variation of sudden death rate in patients with myocardial infarction. Beta blockers, or drugs with beta blocking effects, are known to prevent sudden cardiac death. It was unclear if the cardiac nerves in the heart play only a passive role in the mechanisms of sudden death. To determine if nerve sprouting and neural remodeling occur after myocardial infarction, we performed immunocytochemical studies of cardiac nerves in explanted native hearts of transplant recipients. We found that there was a positive correlation between nerve density and a clinical history of ventricular arrhythmia. Encouraged by these results, we performed a study in dogs to determine whether or not nerve growth factor (NGF) infusion to the left stellate ganglion can facilitate the development of ventricular tachycardia (VT), ventricular fibrillation (VF), and sudden cardiac death (SCD). The results showed that augmented myocardial sympathetic nerve sprouting through NGF infusion plus atrioventricular (AV) block and MI result in a 44% incidence (four of nine dogs) of SCD and a high incidence of VT in the chronic phase of MI. In contrast, none of the six dogs (with AV block and MI) without NGF infusion died suddenly or had frequent VT episodes. Based on these findings, we propose the nerve sprouting hypothesis of ventricular arrhythmia and SCD. The hypothesis states that MI results in nerve injury, followed by sympathetic nerve sprouting and regional (heterogeneous) myocardial hyperinnervation. The coupling between augmented sympathetic nerve sprouting with electrically remodeled myocardium results in VT, VF and SCD. Modification of nerve sprouting after MI may provide a novel opportunity for arrhythmia control.

Keywords: Autonomic nervous system; Infarction; Ion channels; Remodeling; Sudden death; Ventricular arrhythmias

1. Introduction

The nerve sprouting hypothesis of sudden cardiac death states that MI results in nerve injury, followed by sympathetic nerve sprouting and regional myocardial hyperinnervation. The coupling between augmented sympathetic nerve sprouting with electrically remodeled myocardium results in VT, VF and SCD. Modification of nerve sprouting after MI may provide a novel opportunity for arrhythmia control. In this article we will review the evidence in support of the nerve sprouting hypothesis of sudden cardiac death.

2. Cardiac nerves

The first descriptions of cardiac innervation were made in the mid-19th century by Ludwig [1] and Bidder [2] in...
studies of the frog’s heart. Since then, the autonomic innervation of the vertebrate heart has been studied extensively [3]. Hearts are innervated by both sympathetic and parasympathetic nerves. Cardiac sympathetic innervation includes nerves from both cervical and thoracic sympathetic ganglia. The postganglionic efferent fibers in the sympathetic cardiac nerves arise in the sympathetic trunk ganglia. Therefore, the sympathetic nerves do not make synaptic connections within the heart. The sympathetic innervation to the ventricles follows a course along the common pulmonary artery into the plexus supplying the main left coronary artery. The sympathetic nerves are distributed to the myocardium in superficial epicardial layers. They penetrate the myocardium along with the coronary arteries [4,5]. The parasympathetic innervation to the heart comes from the vagus nerve. The efferent component of the vagal branches to the heart includes preganglionic fibers. In contrast to sympathetic innervation, the parasympathetic nerves do make synaptic connections with ganglion cells in the cardiac plexus or intracardiac ganglia. Like other peripheral nerves [6], many cardiac nerves have a sheath of Schwann. However, there are also nonmyelinated fibers in the heart.

Recent advancements in immunocytochemical techniques have allowed investigators to stain the Schwann cells using the antibody to the S100 protein [7,8] and to stain the autonomic nerves using antibodies against nerve-specific markers such as neurofilament, synaptophysin (SYN), tyrosine hydroxylase (TH), protein gene product 9.5, and many others [9–13]. Chow et al. [14] studied the effects of death on the immunofluorescence of autonomic nerves supplying the human ventricular myocardium. Percutaneous myocardial samples were obtained up to 5–11 days after death. The authors showed that immunocytochemical techniques could be used on human hearts to detect cardiac nerves up to 6 days after death [14]. Those studies indicate that it is possible to study the cardiac nerves using immunocytochemical techniques in animal models and in human autopsy specimens. Using these techniques, Marron et al. [11] examined the entire endocardial and epicardial surfaces of infant and adult hearts obtained postmortem and at transplantation. Nerve fiber terminals were identified in the atrial endocardium, epicardium, and coronary sinus. These terminals displayed immunoreactivity for tyrosine hydroxylase, neuropeptide Y, and the general neural marker protein gene product 9.5. Acetylcholinesterase activity was detected in <5% of endocardial terminals and in no epicardial terminals arising from myelinated fibers. A distinct population of terminals was demonstrated to arise from nonmyelinated fibers in the endocardial plexus of the atria and left ventricle and were predominantly acetylcholinesterase-positive. These data indicate that autonomic nerve fibers are widely distributed in the human myocardium. Nerve fibers containing acetylcholine and catecholamines may be important in regulating both the mechanical and the electrical activity of the heart.

Table 1 shows a summary of the stains used in our laboratory.

### Table 1

<table>
<thead>
<tr>
<th>Stain</th>
<th>Specific for</th>
<th>Utility*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100 protein</td>
<td>Schwann cells</td>
<td>Most useful stain for old, formalin-fixed human cardiac tissues</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>Sympathetic nerves</td>
<td>To identify sympathetic nerves or structure that contains tyrosine hydroxylase</td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>Parasympathetic nerves</td>
<td>To identify parasympathetic nerves and intracardiac parasympathetic ganglia</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Nerve synapses</td>
<td>To identify cardiac nerves</td>
</tr>
<tr>
<td>Neurofilament</td>
<td>Nerve axons</td>
<td>To identify cardiac nerves</td>
</tr>
<tr>
<td>Protein gene product 9.5</td>
<td>Nerves</td>
<td>To identify growing nerves. Expected to be positive in nerve sprouting. The nerves that stain positive for GAP43 may not be mature enough to express tyrosine hydroxylase</td>
</tr>
<tr>
<td>Growth associated protein 43</td>
<td>Growth cones of sprouting axons</td>
<td></td>
</tr>
</tbody>
</table>

*Two major factors that may affect the results: (1) antibody specificity. For example, rabbit anti-cow S100 antibody that was extremely useful in staining paraffin-fixed human cardiac tissue blocks often failed to stain canine cardiac tissues. (2) Overfixation with formalin may result in loss of antigenicity with tissue processing (for example, use of formalin-fixed paraffin embedded tissues rather than frozen sections). We use 4% formalin for 45–60 min, followed by storage in 70% alcohol for best results.

3. Left and right functional asymmetry of cardiac innervation

Cardiac sympathetic innervation shows significant functional asymmetry [15–20]. Stimulating right sympathetic nerves results in an increased heart rate due to the activation of sinus node. It also decreases vulnerability to arrhythmia. In contrast, stimulating left sympathetic nerves results in a prominent increase of blood pressure and a significant increase of ventricular vulnerability to fibrillation. While right stellate ganglion stimulation is characterized by an increase of heart rate and left stellate ganglion stimulation an increase of contraction and blood pressure, this functional asymmetry is not absolute. Brandys et al.
nerve sprouting also occurs after MI. Compatible with this or coronary occlusion. To date, there exists no high-yield myocardial ischemia [33], it is reasonable to expect that and the increased incidence of SCD was not related to MI system after brain injury [31,32]. model; many deaths are sudden. However, there was no with abnormal nerve sprouting in the central nervous gene, R400Q. There is a high mortality rate (44%) in that etiology of injury-related epilepsy, which is associated a common point mutation in the cal environment. This sequence of events may account for model for human hypertrophic cardiomyopathy caused by functional synapses and permanently alter the physiologi- Recently, Marian et al. [47] reported a transgenic rabbit to reinnervate the end organ. Some of the spouts may form nerability to SCD develops after suffering from MI.

Left and right sympathetic imbalance has been implicated in the sudden infant death syndrome (SIDS). Schwartz [23] suggested that prolongation of the QT interval in SIDS [24] may depend on developmental alterations in cardiac sympathetic innervation. Because the right and left sympathetic nerves may occasionally develop at different rates, it leads to an imbalance that might be arrhythmogenic [25].

4. Nerve sprouting after myocardial infarction

Following division, crushing, interference of blood supply, or other means of injury to a nerve, the peripheral nerves undergo Wallerian degeneration [6], which may be followed by neurilemma cell proliferation and axonal regeneration. The axonal regeneration is initially slow, but accelerates to reach a constant rate by the third day after injury [26,27]. However, the rate may vary depending on the injury type, age, and species. Estimates of the rate of regeneration vary between 1 and 3 mm/day [26,27]. In unconditioned rat sciatic nerve, for example, the regeneration rate is 3.2 mm/day [27]. The regeneration effort is triggered by the reexpression of nerve growth factor (NGF) or other neurotrophic factor genes in the non-neural cells around the site of injury [28]. For example, there is a significant increase of NGF activity in the Schwann cells of the sympathetically-denervated rat iris [29]. It has also been demonstrated that Interleukin-1 released by macrophages plays a role in the augmented local production of NGF after peripheral nerve injury [30]. The NGF originated from non-neural cells then results in nerve sprouting during which the neural cells produce sprouts in an effort to reinnervate the end organ. Some of the spouts may form functional synapses and permanently alter the physiological environment. This sequence of events may account for the etiology of injury-related epilepsy, which is associated with abnormal nerve sprouting in the central nervous system after brain injury [31,32].

Because nerves in the ventricles may be injured during myocardial ischemia [33], it is reasonable to expect that nerve sprouting also occurs after MI. Compatible with this expectation, necrotic injury to the rat myocardium results in denervation followed by proliferative regeneration of Schwann cells and axons [34]. Abnormal patterns of neurilemma proliferation have been documented in infarcted human and rat hearts [7,8]. Using I-123-metiodobenzylguanidine scanning, both denervation and reinnervation have been demonstrated in humans and dogs after MI [35–37]. The functional significance of reinnervation after MI is unclear. Vracko and co-workers [7,8] suggested that abnormal patterns of myocardial innervation may cause ventricular arrhythmia. However, no data were presented to support that hypothesis. On the other hand, in patients with cardiac transplantation, reinnervation is associated with significant improved exercise performance determined by heart rate, anaerobic threshold and oxygen uptake [38]. These data suggest that nerve sprouting occurs after MI and cardiac transplantation, and that it may contribute to the increased hemodynamic performance of the surviving myocardium. However, excessive nerve sprouting may result in abnormal patterns of myocardial innervation and may potentially increase cardiac arrhyth-

5. Animal models of sudden cardiac death

There are a number of experimental models [17,19,39–43] in which ventricular tachyarrhythmias have been provoked in the presence or absence of structural alterations imposed on the myocardium. However, the investigators induced ischemia or provided artificial ‘triggers’ such as electrical stimulation or drugs, to induce VT or VF. If these perturbations were not performed, the probability of SCD in dogs after MI was low. For example, Hunt et al. [44] reported a study in which 97 dogs were subjected to LAD ligation and followed for up to 4 months. Sponta-

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animal model in which SCD caused by VF occurs spontaneously in chronic MI [18–20].

6. Electrical and anatomical remodeling after MI

Because most SCDs occur in patients with coronary artery diseases and MI, the electrical and anatomical remodeling created by infarction may play an important role in the pathogenesis of VF and SCD. In experimental models, permanent occlusion of the LAD causes the development of transmural anteroseptal infarction [40]. The surviving rim of myocardial fibers (few to several hundred cells thick) on the epicardial surface of a transmural infarct is known as the epicardial border zone (EBZ) [48]. The EBZ has been shown to be the frequent site of origin of inducible VT/VF 1 week after LAD occlusion (healing phase of MI) [49,50]. In the first week after LAD occlusion, myocardial remodeling leads to increased connective tissue, collagen and edema between the epicardial muscle bundles, resulting in non-uniform anisotropy [48]. Active membrane properties of EBZ are altered. Peak L-type inward calcium current is reduced in myocytes isolated from the EBZ [51], and the recovery of the fast inward sodium current is delayed [52]. The changes in active membrane properties lead to altered excitability and post-repolarization refractoriness in the EBZ, promoting conduc tion block and reentry either during premature stimulation or during rapid pacing [49,50,52]. Electrical remodeling is not limited to the EBZ. Significant changes may also occur in non-infarcted myocardium. Qin et al. [53] demonstrated that MI might result in hypertrophy, action potential duration (APD) prolongation and marked heterogeneity of the time course of repolarization in the non-infarcted myocardium. These changes could be explained by the reduction of transient outward K+ currents. Aimond et al. [54] subjected young rats to left coronary ligature. After 4–6 months, they studied enzymatically dissociated ventricular cells. They found that long-term coronary ligation resulted in a significantly altered L-type calcium current, including reduced peak amplitude and a slower inactivation. They also found a significantly altered K+ current in post-MI cells. These findings indicate that MI results in significant electrical remodeling in both the EBZ and other non-infarcted myocardium [55].

7. Electrical remodeling due to complete AV block

Significant alterations of heart rate can result in electrical remodeling and increased vulnerability to ventricular arrhythmia. Vos et al. [43] first reported that, when challenged with d-sotalol, dogs with chronic AV block and ventricular hypertrophy may develop torsade de points (TdP) VT. These proarhythmic effects were due to the electrical remodeling that occurs after complete AV block [45,56]. The electrical remodeling includes downregulation of delayed rectifier K+ currents IKs and IKr in the myocardium, which delays repolarization, prolongs the QT interval, and thereby predisposes the myocardium to the acquired TdP [57,58]. While AV block and bradycardia cause electrical remodeling, it is interesting to note that rapid pacing, which results in heart failure, can also result in electrical remodeling, including downregulation of (Ito) and action potential prolongation [42]. CsCl, which inhibits its repolarizing K+ currents that are downregulated during heart failure, results in a larger prolongation of APD in these dogs than in normal controls.

8. The interaction between nerve sprouting (neural remodeling) and electrical remodeling

β-Adrenergic stimulation is known to increase ionic current through L-type calcium channels (ICa), IKs, and chloride channels [ICl(Ca) and ICl-cAMP] [59,60]. The increased IKs tends to shorten APD while the increased ICa tends to prolong APD. In the normal canine ventricles in vivo, sympathetic stimulation results in shortening of APD and decreasing dispersion of refractoriness [61], implying that there is a net increase of outward repolarizing currents IKs and ICl versus the inward current ICa. However, the same is not true when IKs is suppressed or downregulated [62]. In the perfused canine tissues, chromanol 293B (a specific IKs blocker) prolongs the QT interval and APD90 of all myocardial cells but does not widen the T wave or induce TdP. Isoproterenol in the continued presence of chromanol 293B abbreviated the APD90 of epicardial and endocardial cells but not that of the M cells, resulting in widening of the T wave and a dramatic accentuation of dispersion of repolarization. Spontaneous as well as programmed electrical stimulation-induced TdP was observed only after exposure to the IKs blocker and isoproterenol. The IKs is also abnormal in patients with type I congenital long QT syndrome (LQT1) [63–65]. During exercise testing, these patients had diminished chronotropic response and paradoxical prolongation of QT interval [66]. Epinephrine may induce TdP, while β-blocker therapy and left-sympathectomy are anti-arrhythmic in patients with LQT1 [65,67]. Kadish et al. [68] reported that in patients with a history of polymorphic VT in response to type Ia antiarrhythmic agents, exercise testing at drug-free state can result in paradoxical lengthening of the QT interval. In contrast, only one of the 11 control patients had QT lengthening with exercise. Half of the patients in that study had coronary artery diseases. These data suggest that sympathetic stimulation is arrhythmogenic if the IKs is genetically abnormal (such as in the congenital long QT syndrome), inhibited by pharmacological agents, or downregulated. Sympathetic stimulation in these ventricles may increase the dispersion of repolarization and the TdP arrhythmia. The mechanism is most
likely related to a large augmentation of residual IKs in epicardial and endocardial cells but not in M cells, in which IKs is intrinsically weak [62]. This hypothesis may explain the mechanism by which an abnormally prolonged QT interval is a predictor of cardiovascular mortality after MI [69].

If an interaction between sympathetic stimulation and reduction of IKs is important in cardiac arrhythmogenesis and SCD, then left stellectomy, which removes or reduces cardiac innervation, should be effective in preventing cardiac arrhythmia. Compatible with this hypothesis, left stellectomy in general have been shown to be antiarrhythmic. In both human patients and in animals, left stellectomy is effective in the prevention of SCD after MI [70], which had acquired abnormalities of potassium channels due to electrical remodeling. In type I congenital long QT syndrome, the abnormal potassium channel activity was genetic rather than acquired. However, left stellectomy was also useful (although not 100% effective) in preventing the recurrence of cardiac events [67]. These results show that an interaction between abnormal electrophysiological substrate and sympathetic stimulation is important in cardiac arrhythmogenesis. Removing cardiac sympathetic nerves might be partially effective in preventing SCD.

While many studies have been performed on the mechanisms of electrical remodeling after MI, there is little information available on the importance and arrhythmogenic potentials of sympathetic nerve sprouting after MI. To demonstrate the importance of nerve sprouting on arrhythmogenesis, we studied the explanted native hearts of human transplant recipients. We also performed a prospective study to determine whether or not augmented sympathetic nerve sprouting increases the incidence of SCD in a canine model. Here we provide a brief summary of these studies.

9. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia in humans

We [71] studied 53 native hearts of transplant recipients. History was reviewed to determine the presence (group A) or absence (group B) of ventricular arrhythmias (including both VT and a history of sudden cardiac death). Immunocytochemical staining for S100 protein, neurofilament protein, tyrosine hydroxylase and protein gene product 9.5 was performed to study the distribution and the density of sympathetic nerves. A total of 30 patients had documented ventricular arrhythmias including unsustained or sustained ventricular tachycardia and SCD. Regional increase of sympathetic nerves was observed around the diseased myocardium and blood vessels in all 30 hearts. Fig. 1 shows an example of positive S100 protein staining of cardiac nerves (arrows) between normal (N) and scar tissues (SC). The density of nerve fibers was significantly higher in group A patients than in group B patients. We conclude that there is an association between a history of spontaneous ventricular arrhythmia and an increased density of sympathetic nerves in patients with severe heart failure. These findings suggest that abnormally increased post-injury sympathetic nerve density may be in part responsible for the occurrence of ventricular arrhythmia and SCD in these patients.

10. Nerve sprouting and sudden cardiac death in dogs

We [72] hypothesized that induction of increased sympathetic nerve sprouting by nerve growth factor (NGF) infusion to the left stellate ganglion in dogs with complete AV block [45,56] and MI may increase the frequency of ventricular arrhythmia and SCD. The augmented sympathetic nerve sprouting would provide increased sympathetic innervation to the myocardium. The AV block and MI would result in electrical remodeling. An interaction between nerve sprouting (neural remodeling) and electrical remodeling may result in a high-yield animal model of spontaneous SCD after MI. The purpose of the present study was to test this hypothesis.

The first step was to prove that NGF infusion to the left stellate ganglion could result in nerve sprouting. In three normal dogs, we infused NGF to the left stellate ganglion via an Alzet osmotic pump over a period of 2 weeks. Immunocytochemical studies showed that this method successfully induced sympathetic nerve sprouting in the ventricles. We then proceeded with the experiments in which dogs underwent the following procedures: AV block was induced by radiofrequency catheter ablation of the AV junction. MI was created by ligation of the LAD below the first diagonal branch. An implantable cardioverter-defibrillator (ICD) was implanted to detect VT and VF. In nine dogs with MI and complete AV block, we also infused
nerve growth factor (NGF) to the left stellate ganglion via an osmotic pump (experimental group). Another six dogs with MI and complete AV block but without NGF infusion served as controls. Immunocytochemical staining revealed greater sympathetic nerve sprouting in the experimental group than in the control group.

All dogs showed spontaneous VT after MI (phase-1 VT). Spontaneous VT reappeared 13.1±6.0 days after surgery (phase-2 VT). The frequency of phase-2 VT was significantly higher in the experimental group than in the control group. In the experimental group, the occurrence of phase-2 VT shows a significant (P<0.05) diurnal variation with the peak incidence in the morning to early afternoon. Four dogs in the experimental group but none in the control group died suddenly of spontaneous VF. In an additional six dogs we created MI without producing AV block or infusing NGF. All six dogs showed histological evidence of sympathetic nerve sprouting 48±5 days later. However, none of these six dogs died suddenly.

It is interesting to note that the nerve density in patients with ventricular arrhythmia (19.6±11.2/mm²) [71] overlaps with the nerve density in the experimental group of the present study. Also, in dogs with MI only (without AV block and NGF infusion), there is also evidence of nerve sprouting. These results suggest that cardiac nerve sprouting may occur after MI even without exogenous NGF. Infusion of NGF accelerated and intensified the magnitude of nerve sprouting, resulting in a high incidence of SCD. Another interesting finding is that NGF infusion to the left stellate ganglion in normal dogs resulted in nerve sprouting but did not result in ventricular arrhythmia or SCD. In the control group of dogs, electrical remodeling induced by AV block and MI also failed to result in SCD. An interaction between nerve sprouting (neural remodeling) and electrical remodeling is needed to create a high-yield canine model of VT, VF, or SCD.

As stated above, the only other canine model of SCD in which VF occurs spontaneously was the German shepherds with inherited ventricular arrhythmias [46,73]. In that model, heterogeneous sympathetic innervation was consistently identified [74]. Furthermore, there was a heterogeneous increase of beta-receptor density. Isolated anteroseptal M cell preparations of afflicted dogs studied with microelectrodes showed abnormal lengthening, rather than shortening of action potential duration in response to isoproterenol infusion [75]. These results imply that in the German shepherd model of SCD, the mechanisms of death might also be related to an interaction between heterogeneous sympathetic innervation and abnormal electrical substrate, most likely due to the presence of abnormal potassium channels [76].

11. Clinical implications

Nerve sprouting hypothesis explains the efficacy of β-blockers in the prevention of SCD [77,78]. It may also explain the results of some clinical trials. For example, sotalol, a drug with β-blocking effects, is known to be effective in preventing ventricular arrhythmias in patients with chronic MI [79]. If the β-blocking activity is removed (such as in d-sotalol), then the drug increases mortality in patients with MI [80]. Future development of antiarrhythmic interventions should target not only the electrical remodeling, but also the neural remodeling (sympathetic nerve sprouting and hyperinnervation) after MI.

It is also known that left stellectomy is effective in the prevention of SCD after MI both in animal models and in humans [70,81,82]. These findings are also compatible with the nerve sprouting hypothesis of SCD.

12. Conclusions

We conclude that sympathetic hyperinnervation occurs in some (but not all) patients after MI. There is an association between sympathetic hyperinnervation and ventricular arrhythmia. NGF infusion to the left stellate ganglion in dogs with chronic MI and AV block increases sympathetic nerve sprouting and creates a high-yield model of spontaneous VT, VF, and SCD. The magnitude of sympathetic nerve sprouting may be an important determinant of SCD in chronic MI. These results support the nerve sprouting hypothesis of sudden cardiac death.

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