Sympathetic Nervous System Activity and Ventricular Tachyarrhythmias: Recent Advances

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Sympathetic nervous system activity (SNSA) is believed to participate in the genesis of ventricular tachyarrhythmias (VTA) but understanding has been impeded by the number and complexity of effects and the paucity of data from humans. New information from studies of genetic disorders, animal models, and spontaneous human arrhythmias indicates the importance of the temporal pattern of SNSA in arrhythmia development. The proarrhythmic effects of short-term elevations of SNSA are exemplified by genetic disorders and include enhancement of early and delayed afterdepolarizations and increased dispersion of repolarization. The role of long-term elevations of SNSA is suggested by animal models of enhanced SNSA signaling that results in apoptosis, hypertrophy, and fibrosis, and sympathetic nerve sprouting caused by infusion of nerve growth factor. Processes that overlap short- and long-term effects are suggested by changes in R-R interval variability (RRV) that precede VTA in patients by several hours. SNSA-mediated alterations in gene expression of ion channels may account for some intermediate-term effects. The propensity for VTA is highest when short-, intermediate, and long-term changes are superimposed. Because the proarrhythmic effects are related to the duration and intensity of SNSA, normal regulatory processes such as parasympathetic activity that inhibits SNSA, and oscillations that continuously vary the intensity of SNSA may provide vital antiarrhythmic protection that is lost in severe heart failure and other disorders. These observations may have therapeutic implications. The recommended use of β -adrenergic receptor blockers to achieve a constant level of inhibition does not take into account the temporal patterns and regional heterogeneity of SNSA, the proarrhythmic effects of α -adrenergic receptor stimulation, or the potential proarrhythmic effects of β -adrenergic receptor blockade. Further research is needed to determine if other approaches to SNSA modulation can enhance the antiarrhythmic effects.

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A wealth of evidence supports the widely held belief that sympathetic nervous system activity (SNSA) participates in the genesis of ventricular tachyarrhythmias (VTA) and sudden death. Catecholamines exert potentially proarrhythmic electrophysiological effects on myocardial tissue.¹ Animal experiments demonstrate a relationship between autonomic nervous system activity and vulnerability to VTA.^{1–6} Agents that block β -adrenergic activity inhibit the development of VTA in animal models.^{7,8} Persuasive evidence that the importance of SNSA is relevant to the care of patients is supported by clinical trials. The Metoprolol CR XL Randomized Intervention Trial In Congestive Heart Failure (MERIT-HF), for instance, showed that β -blocker treatment reduced all-cause mortality by 34% and sudden death by

41%.⁹ Nevertheless, there persisted a 7.2% death rate per year, most of which (approximately 55%) was sudden and presumably arrhythmic. Thus, the protection conferred by β -blockers is incomplete. The Cardiac Arrest Study Hamburg (CASH) included a β -blocker (metoprolol) treatment arm; β -blockers were not permitted in the other two groups.¹⁰ All-cause and sudden death mortality was the highest in the metoprolol group (45.4% and 35.1%, respectively, mean follow-up: 57 $\pm$ 34 months), although this was just slightly, but not significantly, greater than in the amiodarone group (43.5% and 29.5%, respectively). In the primary analysis, the outcomes of patients in the amiodarone and metoprolol treatment arms were combined and compared to patients who received implantable cardioverter defibrillators

(ICDs). All-cause mortality was 23% less in the ICD group, but this did not achieve statistical significance.¹⁰ On the other hand, ICDs provided significantly better protection against sudden death (crude sudden death rate: 13.0%) than the combined group (33.0%). These findings suggest that β -blockers do not provide satisfactory protection against sudden death when compared to ICDs in survivors of cardiac arrest.

There are several possible explanations for the incomplete protection of β -blocker therapy: (1) The sympathetic nervous system does not participate in all VTA; (2) β -blocker concentration at the effector sites is inadequate due to pharmacokinetic interference, inadequate dose, or noncompliance; and (3) incorrect antisympathetic effect. Although substantial circumstantial evidence exists, participation of the sympathetic nervous system has not been proven for any human VTA and substantial gaps remain in our knowledge about the effects of SNSA and especially of the impact of SNSA intensity and temporal pattern of activity. This deficit arises, in part, from two major impediments in this area of research. The first is that data about spontaneous human arrhythmias have been very difficult to acquire because of the unpredictable occurrence and often fatal outcome of VTA. The second is that SNSA is involved in so many processes that affect the electrophysiology of myocardial cells and the levels of regulation are so complex that isolation of the individual effects is extremely difficult. Nevertheless, recent research has added substantially to the understanding of the potential effects of SNSA on VTA.

SHORT-TERM EFFECTS OF SNSA

VTA can occur shortly after events associated with a rise in sympathetic activity suggesting that the sympathetic nervous system can initiate or at least facilitate the initiation of VTA over a short period, e.g., in less than 60 minutes. There are many mechanisms by which SNSA can alter myocardial electrophysiological properties that could precipitate VTA. Important effects are those mediated by myocardial ischemia resulting from increased myocardial oxygen demand due to increased heart rate, contractility, or afterload, or from reduced oxygen supply due to vasoconstriction, thrombosis (activation of platelets or hemostatic factors), or plaque rupture due to shear stress or other fac-

tors. Electrophysiological effects could be mediated by myocardial stretch as a consequence of altered blood pressure. It has been demonstrated that the electrophysiological effects of myocardial stretch may be mediated by β -adrenergic stimulation.¹¹ Free radical production has also been reported.^{12,13}

The electrophysiological effects responsible for VTA initiation are also mediated by stimulation of adrenergic receptors on ventricular myocytes involved in the genesis of the arrhythmia. Three major types of adrenergic receptors have been identified: α_1 , α_2 , and β . Of the three subtypes of α_1 -adrenergic receptors (α_{1A} , α_{1B} , and α_{1D}) α_{1A} is the most abundant in the human heart.¹⁴ α_1 -Adrenergic receptors can couple to numerous intracellular signal transduction responses such as phospholipase C and D and numerous ion currents including L-type Ca^{2+} current,¹⁵ the T-type Ca^{2+} current,¹⁶ the transient outward current (I_{to}),¹⁷⁻¹⁹ the delayed rectifier current (I_{K}),²⁰⁻²³ the slow component of the delayed rectifier current (I_{Ks}),²⁴ the inward rectifying current (I_{K1}),²⁵⁻²⁷ and the acetylcholine-activated K^+ current (I_{KAch}). In addition, the Na^+/H^+ exchanger and Na^+ , K^+ -ATPase can be activated.^{21,26}

Three subtypes of α_2 -adrenergic receptors (α_{2A} , α_{2B} , and α_{2C}) exist but their status in human cardiac tissue is uncertain. The known significance of α_2 -adrenergic receptors to cardiac electrophysiology is related to the presynaptic inhibition of norepinephrine release.¹⁴ Intracoronary administration of α_2 -adrenergic receptor antagonists enhances catecholamine spillover in the presence of increased SNSA, e.g., in heart failure.²⁸

There may be up to four β -adrenergic receptor subtypes, but there is little evidence for effects of β_3 - and β_4 -adrenergic receptor subtypes on cardiac electrophysiology. The proportion of β_1 - to β_2 -adrenergic receptors in the human ventricle is approximately 3 to 1. β -Adrenergic receptors selectively couple to the adenylylcyclase stimulatory G protein (G_s). G_s -stimulated adenylylcyclase increases the level of cyclic adenosine monophosphate (cAMP) and activates protein kinase A. Substrates phosphorylated by protein kinase A that may be relevant to cardiac arrhythmias include the L-type Ca^{2+} channel,^{29,30} the cardiac ryanodine receptor type 2 (RyR2), the 1,4,5-triphosphate receptor (IP3R2), the α -subunit of the cardiac sodium channel, the cardiac isoform of the sodium-calcium exchanger ($I_{\text{Na-Ca}}$), K^+

channels (I_{K1} ,²⁷ HERG, and Ca^{2+} -activated I_{Ks} ³¹), Ca^{2+} -activated chloride current ($I_{\text{Cl/Ca}}$),³¹ and $\text{Na}^+/\text{Ca}^{2+}$ exchange current ($I_{\text{Na-Ca}}$).

The effects of SNSA are cell-type specific, dose-dependent, time-dependent, and disease-specific. Burashnikov and Antzelevitch, for instance, showed that in the canine heart α_1 -adrenergic receptor stimulation produces APD prolongation in Purkinje cells and shortening in M cells.²² In epicardial and endocardial myocytes low doses of α_1 -adrenergic agonists caused slight but significant APD lengthening, but APD returned to control levels with higher doses.²² The time-dependent effects of adrenergic stimulation were illustrated by Gaughan et al.³² who showed that the acute application of phenylephrine had no significant effect on neonatal rat myocyte I_{to} whereas I_{to} density was 76% smaller after 72 hours exposure. The effect of disease on the immediate impact of adrenergic stimulation has been demonstrated as discussed below.

The effects of SNSA are further complicated by the interactions with other neuroendocrine systems that affect electrophysiological properties, such as the renin angiotensin and the parasympathetic nervous systems. The interactions are also complex, for instance, SNSA interacts with vagal activity in a time-dependent manner at the central nervous system level, prejunctional, and postjunctional levels.³³

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Because there are an infinite number of perturbations and combinations of changes related to SNSA that could result in generation of arrhythmias, it is important to focus on the effects most likely to be clinically relevant. Genetic disorders may provide insights to the extent that they isolate arrhythmogenic phenomena. CPVT is a potentially fatal disorder of children and adolescents.^{34,35} The same or a closely related disorder, familial polymorphic ventricular tachycardia, has been described in young adults.³⁶ VTA occur reliably within minutes in response to exercise, mental stress, and administration of catecholamines. Treatment with β -blockers is reported to prevent arrhythmias and sudden death.³⁷ VTA in this disorder have a characteristic "bidirectional" configuration, similar to those associated with digitalis toxicity.^{38,39} Because of the similarity to VTA associated with digitalis intoxica-

tion, which is also enhanced by adrenergic stimulation,⁴⁰ it was speculated that CPVT is caused by DADs.^{41,42}

It was recently discovered that a mutation in the genes encoding the ryanodine receptor is responsible for some cases of CPVT.^{43,44} Marx et al.⁴⁵ reported that adrenergic stimulation results in the hyperphosphorylation of RyR2 through phosphokinase A (PKA) that alters channel activity. Although the change in function resulting from the genetic defect has not been identified, the defect probably results in a heightened sensitivity to catecholamines for initiation of DADs. Clearly, the functional change does not substantially interfere with normal development of affected individuals and many normal activities. DADs have been proposed as the mechanism of VTA in other conditions including nonischemic cardiomyopathy as discussed below. Therefore, CPVT may be a model for one mechanism by which VTA can be initiated by the short-term effects of SNSA.

Congenital Long QT Syndrome (LQTS)

The mechanism of torsades de pointes (TdP), the most common VTA observed in patients with congenital LQTS, is not established. Nevertheless, it has long been recognized that TdP and sudden death are often precipitated by activities that increase SNSA in this disorder. Also, effective treatments reduce SNSA to the heart by β -adrenergic receptor blockade and by surgical interruption of left-sided sympathetic nervous input to the heart.^{46,47} The increased action potential duration (APD) that underlies QT prolongation predisposes to early afterdepolarizations (EADs). EADs are augmented by adrenergic activity^{42,48} and seemed to be a plausible mechanism of TdP. On the other hand, this was thought to be unlikely because tachycardia would result in rate-dependent APD shortening and reduce the propensity for sustained EADs. It has also been proposed that EADs could enhance heterogeneity of repolarization by regional variation of the APD prolongation effect that occurs when EADs do not reach the threshold.⁴² EADs could also initiate VTA if the underlying conditions for reentry were present. However, if adrenergically induced EADs caused TdP, it remained to be explained why β -adrenergic blocking drugs were not always effective.⁴⁶

The discovery of multiple subtypes of LQTS was followed by the recognition that the context of

arrhythmic events differed between the subtypes. Ali et al.⁴⁹ examined cardiac events related to acute arousal caused by exercise, swimming, emotion, or noise. Arousal-related cardiac events occurred in 85% of long QT syndrome type 1 (LQT1), 67% of type 2 (LQT2), and 33% of type 3 (LQT3) patients. Although overlap exists, the pattern that has emerged is that physical activity is associated with cardiac events in LQT1 patients, sudden auditory stimuli precede events in LQT2 patients whereas events tend to occur during sleep in LQT3 patients.⁴⁹⁻⁵³ These observations suggested that the response to SNSA differs between the LQTS subtypes. Using pharmacological models of the three major subtypes of LQTS in an arterially perfused canine myocardial wedge preparation, Shimizu and Antzelevitch⁵⁴ discovered that the principal arrhythmogenic effect of SNSA was the alteration of dispersion of repolarization. The susceptibility to TdP in the three models was assessed by either spontaneous occurrence or induction using programmed electrical stimulation. LQT1 was modeled by blockade of I_{Ks} by chromanol 293B. In this model APD was homogeneously prolonged in all three major cell types, i.e., epicardial, midmyocardial (M), and endocardial ventricular myocytes. Under these conditions, TdP was not observed. Isoproterenol, a β_1 - and β_2 -adrenergic agonist, augmented APD prolongation of the M cells whereas it shortened APD in epicardial and endocardial cells, thus markedly enhancing the dispersion of repolarization across the myocardium. This resulted in spontaneous and inducible TdP with about equal rates at 2 and 10 minutes after isoproterenol perfusion. This is consistent with the observation that TdP and sudden death often occur in response to physical activity in patients with LQT1. The addition of propranolol in the absence and presence of isoproterenol eliminated the susceptibility to TdP.

Blockade of I_{Kr} by d-sotalol, which was used to mimic LQT2, caused preferential APD prolongation of M cells thereby increasing dispersion of repolarization. This was accompanied by spontaneous and induced TdP in some of the preparations. A biphasic effect was observed with the addition of isoproterenol. Further prolongation of the M cell APD was observed at 2 minutes but was followed by APD abbreviation in the M cell back to control (presotalol) levels by 10 minutes. Greater dispersion of repolarization and increased susceptibility to TdP occurred at 2 minutes after application of isoproterenol. However, 10 minutes after isopro-

terenol the dispersion of repolarization fell to levels close to control values accompanied by a diminution of TdP. The addition of propranolol in the absence or presence of isoproterenol did not affect dispersion of repolarization or TdP in this model. The investigators speculated that the time-dependent change in M cell APD resulted from a faster increase in I_{Na-Ca} than I_{Ks} . In this model, SNSA was presumed to cause VTA by simultaneously increasing heterogeneity of repolarization and enhancing EADs that initiate reentry.^{54,55} The time course of this effect is short (less than or equal to 2 minutes) and transient (less than 10 minutes). The short-lived nature of the vulnerable period produced by SNSA could explain why arrhythmic events in patients with LQT2 occur shortly after a startle stimulus, i.e., an arrhythmia either occurs during a short period after a stimulus or not at all.

The LQT3 model was generated by augmentation of the late sodium current (I_{Na}) by ATX II. This resulted in APD prolongation of all layers with a proportionately greater prolongation in M cells so that dispersion of repolarization was greater than in the LQT1 and LQT2 models. This was associated with a high frequency of spontaneous and inducible TdP. Isoproterenol reduced the degree of repolarization dispersion and the frequency of TdP at 2 minutes and 10 minutes with the greater reduction observed at 10 minutes. Propranolol restored both the dispersion of repolarization and the high frequency of TdP. In other words, in the LQT3 model, β -adrenergic stimulation protected against TdP whereas β -adrenergic blockade removed the protective effect of sympathetic activity. These observations could explain the observation that arrhythmic events in patients with LQT3 often occur during sleep and rarely during physical activity or in response to startle events.

The short-term effects of SNSA observed in LQTS probably extend to more common disorders including those with (1) changes in ion channel function similar to LQTS,⁵⁶ (2) changes in the regional distribution of ion channel function,⁵⁶ and (3) alterations in the regional distribution of sympathetic nerves⁵⁷⁻⁵⁹ and (4) after myocardial infarction.⁶⁰ It is conceivable that disease-related changes in electrophysiological properties could result in a paradoxical antiarrhythmic effect of increased SNSA and proarrhythmic effect of β -adrenergic receptor blocking drugs that mimic the LQT3 model. This could account for some of the failures of β -blockers to prevent sudden death.

LONG-TERM EFFECTS OF SYMPATHETIC ACTIVITY

Some of the factors that increase susceptibility to VTA in acquired disorders occur over relatively long periods of time. For instance, the median time between the last myocardial infarction and the first occurrence of a sustained VTA was approximately 6 years in the Electrophysiological Study Versus Electrocardiographic Monitoring Trial.⁶¹ Several structural changes in myocardial tissue are believed to facilitate VTA. Cell death and confluent scar tissue create barriers to propagation that underlie some forms of reentry.⁶² Interstitial fibrosis is associated with disruption of gap junctions that produce nonuniform anisotropic conduction, reduced safety factor, and loss of electrotonic modulation of repolarization times that may contribute to both macro- and microreentry.^{63–65} Myocardial hypertrophy and heart failure are associated with electrophysiological changes that predispose to VTA.^{59,66}

The association among chronic elevations in sympathetic activity, myocardial dysfunction, VTA, and sudden death has been recognized for several years,^{67,68} whereas therapy with β -blockers improves left ventricular function and reduces the risk of sudden death.⁶⁹ That high levels of SNSA can cause pathological changes was demonstrated many years ago.⁷⁰ Recent research in transgenic mouse models demonstrates that overexpression of elements of adrenergic pathways results in cardiomyopathic phenotypes. For instance, mice overexpressing β_1 -adrenergic receptors demonstrate large areas of interstitial replacement fibrosis, marked myocyte hypertrophy, myofibrillar disarray, and cell death.^{71,72} Overexpression of β_2 -adrenergic receptors also results in cardiomyopathy but much higher levels of expression and longer observation periods are required compared to mice overexpressing β_1 -adrenergic receptors.⁷³ Overexpression of the α_{1B} -adrenergic receptor results in the development of dilated cardiomyopathy with enlargement of all four cardiac chambers and cardiomyocyte disarray in the failing hearts.⁷⁴ After 1.5 years mice with overexpression of the adrenergic receptor stimulatory G-protein (G_{α}) developed myocyte apoptosis, necrosis, hypertrophy, interstitial fibrosis, cardiac dilatation, blunted heart rate variability, reduced baroreflex activity, and a mortality of 45%.^{75–78} Long-term administration of propranolol reversed all these abnormalities.⁷⁸ Overexpression of nerve growth factor resulted in

increased nerve density and norepinephrine content.^{79,80} Accompanying these changes were increased cardiac mass, myocyte hyperplasia, and interstitial fibrosis.^{79,80}

Myocyte apoptosis appears to be mediated by the β_1 -adrenergic receptor with activation of calcineurin via increased intracellular calcium through L-type channels⁸¹ and is inhibited by β -adrenergic receptor blockade.⁷⁸ Stimulation of β_2 -adrenergic receptors are antiapoptotic.⁸² However, there are likely to be several other pathways modulating the proapoptotic process in myocardial tissue that might alter the effects mediated by adrenergic stimulation.⁸³ Catecholamines increase free radical production that may be cytotoxic. These effects are inhibited by β -blocking drugs.^{12,13} Increased adrenergic activity is a major stimulus for pathological myocardial hypertrophy in animal models, an effect mediated by α - and β -adrenergic receptors.^{83,84} Based on clinical studies, it appears that myocardial hypertrophy in patients with heart failure is largely due to β_1 -adrenergic receptors. Treatment with a β_1 -selective blocker with metoprolol⁸⁵ produces reverse remodeling to about the same extent as carvedilol, i.e., a drug with nonselective β -blocker plus α -receptor blocker properties plus antifree radical properties.⁸⁶

INTERMEDIATE-TERM EFFECTS OF SYMPATHETIC ACTIVITY

Arrhythmogenesis has been traditionally framed in terms of triggers and substrate. This was based on the paradigm exemplified by the Wolff-Parkinson-White syndrome whereby a premature beat (trigger) initiated reentry in permanent anatomic components of the reentrant circuit (atrioventricular node, accessory connection, and the intervening myocardium). In the literature, triggers and substrates are rarely strictly defined. However, the definitions must be broad to account for a variety of arrhythmias. The permanent form of junctional reentrant tachycardia, for instance, is often initiated without a premature beat. Instead, tachycardia is preceded by a rise in sinus rate and is probably precipitated by changes in autonomic nervous system activity, which affect the electrophysiological properties of the atrioventricular node and the accessory atrioventricular connection. To accommodate this phenomenon, triggers could logically be extended to include short-term

electrophysiological changes that are required to initiate tachycardia. In patients with sustained monomorphic ventricular tachycardia (SMVT) after myocardial infarction the first episode of tachycardia often develops years after myocardial infarction suggesting that the reentrant circuit develops very slowly and may continue to change. To accommodate disorders in which the underlying anatomy is not permanent, the "substrate" has been extended to include elements of arrhythmogenesis that change slowly. However, newer information indicates that some effects have time courses between short- and long-term that cannot be clearly categorized as "triggers" or "substrates." Although "intermediate-term" is arbitrarily used to describe such effects, it should be recognized that the time course of arrhythmogenesis is a continuum of temporal patterns from immediate to permanent influences.

More than a decade ago Leclercq and colleagues systematically analyzed spontaneous human VTA and provided evidence of sympathetic nervous system involvement in VTA initiation by demonstrating a rise in heart rate before the onset of arrhythmia.⁸⁷ Although the mechanism of facilitation could not be determined, the investigators thought ischemia was unlikely because there were no ischemic ST-T changes on the ECG before the onset of the VTA and it was not prevented by anti-ischemic therapy. We confirmed and extended these findings in a group of patients with SMVT recorded spontaneously on 24-hour Holter tapes in the absence of antiarrhythmic drugs.⁸⁸ Power spectral analysis of the R-R interval time series demonstrated that the rise in heart rate before the onset of SMVT was most likely due to a rise in sympathetic activity, as assessed by changes in the low frequency power. The lack of significant change in the high frequency power suggested that withdrawal of parasympathetic tone was not responsible for the change in heart rate and had no role in the initiation of SMVT.

Leclercq and colleagues⁸⁷ could not exclude the possibility that the sympathetic activity was related to the onset of VTA merely by increasing the frequency of PVCs capable of initiating VTA. However, this could not account for the initiation of SMVT in our study because PVCs could not be shown to initiate VTA in the majority of episodes.⁶³ This suggested that SNSA can initiate reentrant VTA in the absence of a manifest premature beat. Before this, it was assumed that

the initiation of spontaneous SMVT was similar to that observed during programmed electrical stimulation, i.e., due to one or more critically timed PVCs. The initiating PVC had to be early enough in the cycle to encounter conditions suitable for reentry, i.e., unidirectional block due to heterogeneous repolarization. As with programmed stimulation, the initiating PVC would be expected to have an origin and activation sequence different from SMVT. Berger et al. studied the spontaneous onset of SMVT that could be reproduced by programmed stimulation. Half of the cases had the expected initiation sequence, that is, one or more PVCs with a morphology different from that of SMVT, preceded and appeared to cause the initiation of SMVT (type 1 initiation of SMVT). On the other hand, in the other 50% of the cases, the first ventricular complex was identical to subsequent complexes of SMVT (type 2 initiation of SMVT). Berger and colleagues speculated that the mechanism of SMVT initiation in the cases without a trigger PVC resulted from slow conduction of the preceding sinus beat. However, if this were the case, one might expect that PVCs could also initiate SMVT.

In order to further define the role of SNSA in the initiation of SMVT we identified all Holter tapes with a recorded episode of SMVT in the absence of antiarrhythmic drugs from 1646 tapes obtained from patients screened for the ESVEM study.⁶¹ The recordings were digitized, and the configurations of the initial beats of SMVT were compared using a highly specific cross-correlation method. We identified 59 patients with recorded spontaneous SMVT on 24-hour Holter tapes. SMVT onset with an initial ventricular complex that was different from those of SMVT (type 1 onset) comprised only 37% of the patients. The majority of patients (63%) demonstrated type 2 onset, i.e., the first beat of SMVT was identical with subsequent beats. Of course, it is not possible to prove that the type 2 pattern did not result from PVC initiation from a site close to the exit of the reentrant circuit of SMVT and therefore had identical activation sequence and configuration. Two facts suggested that this was unlikely. First, the first ventricular complexes in type 2 onset tended to occur late in the cycle such that coupling intervals were significantly greater than in type 1 SMVT. Second, we have shown that in patients with SMVT due to ischemic heart disease, isolated PVCs with configurations identical to those of SMVT are extremely

rare.⁸⁹ In other words, there was no evidence that the reentrant circuits that underlie SMVT ever produce PVCs with configurations identical to those of SMVT. PVCs should occasionally initiate SMVT if the mechanism suggested by Berger et al. were correct. Surprisingly, despite very frequent PVCs, we found that SMVT with type 2 onset was never observed with a type 1 onset. This was important because it suggested that a process with a potent effect on the electrophysiological properties of the reentrant circuit was responsible for initiating type 2 SMVT.

To address the hypothesis that SNSA was the underlying process that initiated type 2 SMVT, we examined heart rate and power spectral components of the R-R interval variability signal before type 1 and type 2 SMVT.⁹⁰ Up to 4 hours before type 1 SMVT neither heart rate nor any of the power spectral components of the R-R variability signal changed significantly. In contrast, significant changes in heart rate and R-R variability indices suggested a rise in SNSA beginning 2–3 hours before the onset of type 2 SMVT. This suggested that changes in SNSA could have a primary role in the initiation of type 2 SMVT. However, the time course of changes was longer than a traditional trigger but too short to be considered a substrate effect. For this reason it has been characterized as an intermediate-term effect.

There remained some uncertainty regarding the role of SNSA in type 1 SMVT. One possibility was that the role of the SNSA was insignificant and SMVT was precipitated by a PVC. Another theory was that SNSA was already high for at least 4 hours preceding SMVT, but another factor, e.g., a PVC, in addition to elevated SNSA was needed for initiation of type 1 SMVT. In support of the latter theory was the observation that although the heart rate rose gradually in type 1 SMVT and remained unchanged during the 2 hours before onset in type 2 SMVT, the heart rates at the time of SMVT initiation were approximately the same for type 1 and type 2 events.⁹⁰ Therefore, we could not exclude the possibility that the rise in SNSA had preceded the time window available for our analysis.

Further evidence against the concept that the initiation of SMVT was simply due to a short-term effect of SNSA was the observation that there were other times in the same 24-hour period when the

heart rate rose to the same extent without initiating SMVT. None of the linear indices of R-R interval variability provided high specificity for predicting the onset of SMVT. However, the fast Fourier analysis of R-R interval variability used for power spectrum analysis may have some important limitations. It assumes stationary signals whereas we are seeking evidence of changes. In addition, this and most other linear and nonlinear methods of R-R interval variability may not include all of the information available in the series of R-R intervals. To further evaluate changes in R-R interval dynamics preceding the onset of SMVT we used a pattern recognition approach based on the patient's inherent pattern of R-R dynamics. This approach, which was based on modification of the Karhunen-Loeve transform, makes fewer assumptions about the form of changes or the direction of changes. In this investigation, we were able to detect significant deviations from the individual patient's characteristic R-R interval pattern 6.8 ± 4.4 hours (mean $\pm$ standard deviation) before the onset of SMVT with a sensitivity of 70% and a specificity of 93%.⁹¹

The physiologic correlates of deviations from the characteristic R-R pattern have not been examined. Although unproven, sustained elevation of SNSA lasting several hours is compatible with the temporal trends in components of the power spectrum discussed above. There are several processes that could account for an intermediate time course such as that observed before initiation of VTA in our studies. A logical possibility is alteration of electrophysiological properties by changes in ion channel protein expression. Reduction in I_{to} , for example, could be responsible for the increased propensity for VTA.⁹² I_{to} is believed to be responsible for the increased APD in heart failure and hypertrophy and is associated with repolarization heterogeneities.^{93,94} A large portion of I_{to} in human, canine, and rat hearts is encoded by the Kv4.3 gene.⁹⁵ Zhang et al.⁹⁶ reported that decreased transcription of the Kv4.3 gene occurs over a period of hours with a maximum effect by 24 hours in response to α -adrenergic stimulation. In other words, an elevation in SNSA can result in increased APD and increased dispersion of repolarization by α -adrenergic stimulation. These changes could set the stage for the initiation of sustained VTA by short-term effects of SNSA.

ROLE OF SNSA IN VTA ASSOCIATED WITH HEART FAILURE

Although the mechanisms of the VTA that account for a high proportion of deaths in heart failure are unknown, a case can be made for a significant role of the sympathetic nervous system at many points. From the above discussion it is likely that superimposition of effects is a key aspect of SNSA participation in arrhythmogenesis. In other words, short-term elevations of SNSA precipitate arrhythmias in a background of structural changes on account of long-term effects and changes in ion channel expression due to intermediate-term elevations of SNSA. The interaction of several time frames was recently illustrated in a rabbit model of nonischemic heart failure and unsustained VTA.⁹⁷ The arrhythmias in this model are believed to arise from DADs. VTA are rarely observed in the control rabbits but occur spontaneously in the heart failure rabbits. They are enhanced by administration of isoproterenol. The investigators speculated that the heightened propensity for DADs in this model of heart failure was critically related to three factors. The first was upregulation of I_{Na-Ca} . This current was shown to be the carrier of the I_{ti} responsible for the DADs. The increased level of this current increased the I_{ti} response to a given spontaneous release of Ca^{2+} . The second critical change was downregulation of I_{K1} . This resulted in greater depolarization for any I_{ti} , thereby increasing the likelihood that a DAD would generate an action potential. The third essential element was β -adrenergic stimulation that was found to result in electrophysiological changes despite downregulation of the signaling pathways.

Although the time courses and mechanisms of predisposing factors were not investigated in this study, general patterns are apparent. Heart failure in this model was produced by induction of aortic regurgitation followed 2–4 weeks later by aortic constriction. The rabbits were studied approximately 9.5 months after aortic constriction. In an earlier study of the same model, 24-hour monitoring was performed every two weeks after aortic constriction. VTA was first observed at 6 months, but VTA events were consistently observed only after 15 months.⁹⁸ The induction of DADs by β -adrenergic stimulation was a short-term effect obtained by application of isoproterenol. The mechanism by which isoproterenol-enhanced DADs was not examined, but probably resulted from Ca^{2+}

loading by increased L-type Ca^{2+} current or one or more of the other currents discussed above. Upregulation of I_{Na-Ca} has been shown to occur in response to α -adrenergic stimulation within 48 hours of exposure.⁹⁹ Less is known about the time course for the reduction of I_{K1} in this rabbit model. I_{K1} is also reduced in human heart failure.¹⁰⁰ Further reduction of I_{K1} occurs as a short-term response to β -adrenergic stimulation in myocytes from failing human hearts as well as in myocytes from donor hearts.²⁷ Reduction of I_{K1} has been demonstrated to occur after just 3 to 4 weeks in a canine model of heart failure.¹⁰¹

Therefore, in this model of heart failure, SNSA may contribute significantly to the susceptibility to VTA (α -adrenergic stimulation of I_{Na-Ca}) and the short-term initiation of VTA (β -adrenergic stimulation). Although an effect of SNSA on long-term I_{K1} reduction is plausible,¹⁰² this has not been clearly demonstrated. Why VTA did not occur until several months after aortic constriction given the time courses of the three essential factors in other models is unexplained. Sustained VTA and sudden death were not observed in this model, therefore, the link between the arrhythmias examined in this model and malignant VTA remains to be determined. However, based on the temporal pattern observed for spontaneous VTA, it seems likely that additional long-term effects requiring more than 12 months to develop are necessary.

ROLE OF SNSA IN VTA AFTER MYOCARDIAL INFARCTION

Several mechanisms of SNSA interaction in the arrhythmias associated with myocardial infarction have been proposed over the past several decades.^{1,103} The nerve sprouting theory of VTA in the chronic phase of myocardial infarction has added an interesting dimension to arrhythmogenesis. Specifically, Chen et al.¹⁰⁴ proposed that myocardial infarction results in sympathetic nerve injury followed by sympathetic nerve sprouting and heterogeneous myocardial hyperinnervation. This, coupled with other changes due to electrical remodeling, leads to VTA and sudden death. This theory was supported by a study of the hearts of 53 cardiac transplant recipients. The hearts of 30 patients with a history of unsustained VT, sustained VT, or sudden death demonstrated increased density of nerve fibers based on immunocytochemical

staining compared to hearts obtained from patients without VTA.⁵⁷

Cao et al.¹⁰⁵ created a canine model to address the nerve sprouting theory of VTA. Three interventions were used to create the experimental model: (1) complete atrioventricular block, (2) ligation of the left anterior descending coronary artery, and (3) infusion of nerve growth factor (NGF) to the left stellate ganglion (LSG). One set of control animals underwent only the first two interventions (control). All dogs developed phase I VTA (self-terminating) after surgery that persisted for 5.8 ± 2.0 days. Phase II VTA first occurred 13.1 ± 6.0 days after surgery and included all VT occurring until death or sacrifice (up to 60 days after surgery). Phase II VTA was ten times more frequent in LSG dogs (2.0 ± 2.0 episodes/day) than controls (0.2 ± 0.2 episodes/day, $P < 0.05$). Elevations of ventricular and atrial heart rates before the onset of phase II VTA suggested that elevation of SNSA contributed to the genesis of this arrhythmia. Spontaneous ventricular fibrillation developed in four of the nine experimental animals but in none of the six controls. At autopsy, significantly greater nerve density was present in the LSG group. However, there was evidence of nerve sprouting in the control group indicating that this phenomenon occurs after myocardial infarction in the absence of exogenous NGF.

Another report from this group of investigators included data from six dogs using the same model except that NGF was administered to the right stellate ganglion (RSG).¹⁰⁶ Only three dogs in the RSG group developed phase II VTA (compared to all control and LSG dogs). The average number of phase II VTA events in the RSG group was much less (0.01 ± 0.02 episodes/day) than in the other two groups (see above) and none of the RSG animals died suddenly. The differences in VTA and sudden death were observed in spite of a greater degree of myocardial hypertrophy in the RSG group. Significant differences in the corrected QT interval (QTc) were noted in response to administration of NGF. The significant differences were evident as early as two weeks after the infusion of NGF was begun, and appeared to increase until the infusion was discontinued at 5 weeks. QTc increased in the LSG group, decreased in the RSG group, and was intermediate in the control group. Thus, the occurrence of VTA was associated with QTc prolongation. The investigators speculated that the QTc prolongation could be related to increased ex-

pression of L-type calcium channels resulting from sympathetic innervation. In addition, downregulation of I_{Ks} has been reported in dogs with atrioventricular block and myocardial infarction.¹⁰⁷ Sympathetic stimulation under these circumstances can increase dispersion of repolarization and results in TdP as described by Shimizu and Antzelevitch (see above).⁵⁴

The reduction of VTA in the RSG group was another interesting but unexplained observation. This occurred despite greater myocardial hypertrophy in the RSG group. The differential effects of stimulation of the RSG versus the LSG were described more than 30 years ago.¹⁰⁸ Zhou et al. provided two possible explanations for the observed differences in this study. First, they noted that Schwartz¹⁰⁹ suggested that afferent sympathetic fibers from the RSG inhibit sympathetic nerves in the LSG. The authors propose that a similar phenomenon could explain the reduced tendency for VTA in the current study. This presumes that left-sided SNSA is more proarrhythmic than right-sided SNSA. Another mechanism, not suggested by the authors, could be inhibition of LSG by parasympathetic activity. This could only occur if parasympathetic activity was not suppressed by increased RSG (see below). The second explanation offered by Zhou et al.¹⁰⁶ is that RV sympathetic hyperinnervation reduces the electrophysiological heterogeneity between RV and LV. Previous studies have demonstrated differences in left and right ventricular electrophysiological characteristics due, most likely, to greater expression of proteins responsible for I_{to} in the right ventricle. Differences between QT intervals in left and right ventricles were shown to be increased in dogs with chronic atrioventricular block.¹¹⁰ Zhou et al. proposed that RV hyperinnervation results in reduced dispersion of repolarization due to increased QT interval in the right ventricle. This effect could be due to increased current through L-type calcium channels.

The relevance of these findings to human patients remains to be demonstrated. The need for permanent atrioventricular block and infusion of NGF seems "unphysiologic." Nevertheless, the reported findings may reproduce the proarrhythmic process in some patients with myocardial infarction and myocardial hypertrophy who develop vigorous nerve sprouting. The nerve-sprouting theory introduces a new element of time- and region-related patterns of abnormal SNSA. It also opens new therapeutic possibilities, e.g., inhibition of

NGF after myocardial infarction. It also raises potential problems of current approaches. For instance, β -adrenergic receptor blockers could be proarrhythmic in patients with nerve sprouting in the RSG distribution if they produced disinhibition of LSG activity.

ROLE OF SNSA IN DIMINISHING NATURAL PROTECTION AGAINST THE PROARRHYTHMIC EFFECTS OF SNSA

The major purpose of the sympathetic nervous system is to maintain cardiac function on a short-term basis. Although it has been reported that physiological levels of catecholamines induce afterdepolarizations in normal ventricular myocytes,⁴² it is evident that activities and conditions associated with intense sympathetic activity such as competitive sports, trauma, and acute hemorrhage are rarely associated with VTA when cardiac function is normal. Otherwise, this would offset the survival advantage conferred by the powerful compensatory properties of the sympathetic nervous system. However, when long-term compensatory support is needed to meet the demands of organ perfusion due to reduced myocardial contractility or hemodynamic overload, the cardiac adrenergic system becomes maladaptive and can cause changes that increase susceptibility to VTA. The safety mechanisms that prevent VTA at times of intense SNSA in healthy persons and that break down in patients with heart failure are not known. However, it appears from the discussion above that any process that inhibits or reduces SNSA intensity or limits its duration could provide critical protection against the proarrhythmic effects. Although there are several mechanisms that are known to regulate SNSA, little has been documented about the antiarrhythmic effects per se. Nevertheless, there are several candidates for this protective action.

SNSA can be divided into average and rhythmic components. The average component is generally estimated by the net effect, e.g., the average heart rate or burst rate of muscle sympathetic nerve activity. The rhythmic effect consists of a periodic variation in the intensity of SNSA. This oscillatory activity can be detected by power spectral techniques applied to R-R intervals (RRV), muscle sympathetic nerve activity, blood pressure, temperature, and vasomotor activity.¹¹¹⁻¹¹³

Although a range of frequencies is observed, a portion of this oscillatory activity is within the low frequency spectrum (0.04–0.15 Hz) centered around the 0.1 Hz that corresponds to a periodicity of 10 seconds. Because of the strength of the association with SNSA, the absolute or normalized low frequency power (LFP) has been taken to represent SNSA intensity^{114,115} although some controversy exists.¹¹⁶ LFP is relatively low in the resting, supine, healthy person but rises in concert with heart rate in response to maneuvers that increase the average level of SNSA such as upright tilt, exercise, or mental stress.^{114,115} In other words, in normal conditions, the greater the elevation of average SNSA, the greater the variation between the peak and nadir SNSA intensities during oscillatory cycles. To the extent that the oscillation cycle duration remains constant, the time at any given intensity diminishes as the average intensity rises. Several mechanisms for this oscillatory activity have been proposed but recent research points to central nervous system control.¹¹⁷ However, controversy persists and it is not clear if all affected organ systems, in particular ventricular myocardium, are subject to the same type and source of oscillatory activity.

Although the purpose of SNSA oscillation is not known, in patients with VTA due to ischemic heart disease and other disorders associated with reductions in left ventricular function, RRV LFP is diminished despite the elevation in average SNSA.^{68,88,118} Guzzetti and colleagues showed that the amplitude of LFP was related to the severity of left ventricular dysfunction.¹¹⁹ LFP was above normal in patients with increased sympathetic activity associated with mild to moderate left ventricular dysfunction. Patients with more severe cardiac dysfunction, who are known to have higher levels of sympathetic activity, had the lowest values of LFP, consistent with the findings of van de Borne et al.¹¹⁸ The degree of diminution of LFP and other components of RRV has been found to be a predictor of mortality after myocardial infarction.¹²⁰ This is circumstantial evidence that the oscillation of SNSA intensity protects against the proarrhythmic and other adverse consequences of sustained elevations of SNSA. Chronic elevations of SNSA contribute to heart failure and left ventricular dysfunction, which suggest that long-term elevation of SNSA itself may contribute to loss of oscillatory activity.

Recent work suggests that short-term SNSA elevation also may be responsible for diminution

of the oscillation of SNSA in the presence of left ventricular dysfunction. A careful review of data presented by Guzzetti and colleagues showed that head-up tilt in patients with moderate or severe heart failure resulted in a reduction in LFP¹¹⁹ that is in marked contrast to the pattern seen in normal subjects.¹¹⁵ A paradoxical, but unexplained, decline in LFP in response to exercise was also demonstrated in an animal model of congestive heart failure.¹²¹ We found a paradoxical decline in LFP as heart rate increased before the onset of SMVT.¹²² This was particularly characteristic in patients with type 2 onset of SMVT, i.e., those without evidence of PVC initiation.⁹⁰ This suggests that in patients with disturbed left ventricular function short-term rises in SNSA may remove a protective antiarrhythmic effect by diminution in oscillation of SNSA.

The parasympathetic nervous system activity exerts a potent antisymphathetic effect that probably plays an important role in the prevention of the short-, intermediate- and long-term proarrhythmic effects of SNSA. Evidence based largely on the analysis of heart rate and blood pressure responses in animals with normal cardiac function indicates that the effects of parasympathetic activity predominate at rest.¹²³ This inhibits the effects of increased SNSA. However, the inhibitory effects of vagal tone are transient and are lost several seconds after vagal activity diminishes. In the absence of parasympathetic activity, SNSA effects are not only enhanced due to loss of parasympathetic inhibition, but SNSA activity is self-promoting because it inhibits parasympathetic activity thereby preventing its own inhibition. SNSA-induced inhibition of vagal activity lasts nearly 1 hour (in short-term experiments) and it is related to the duration and intensity of preceding SNSA activity.^{124–126} This may be one of the mechanisms by which vagal activity is chronically reduced in patients with chronic left ventricular dysfunction¹²⁷ and one of the mechanisms by which elevated SNSA is maintained. The inhibition of parasympathetic effects is abolished by β -adrenergic blockade drugs but not by α -adrenergic blockade.¹²⁶ This suggests that the benefits of β -blocking drugs are not limited to the interference of the effects of SNSA at the cellular level, but that they have the potential of interrupting the self-promoting enhancement of SNSA by eliminating the inhibition of vagal activity that could, in turn, allow vagally induced inhibition of SNSA.

Long-term processes that reduce SNSA in chronic heart failure such as β -adrenergic receptor down-regulation,¹²⁸ attenuated norepinephrine spillover to exercise and nitroprusside-induced hypotension,^{129,130} and antiapoptotic response of β_2 -adrenergic stimulation,¹³¹ probably provide important protection at the cellular level but they do not reduce SNSA to normal levels, prevent the proarrhythmic effects of short-term elevations of SNSA, or sudden death.

CONCLUSIONS

Significant advances have been made in the understanding of the relationship between SNSA and VTA. The proposed mechanisms by which SNSA increases the vulnerability to VTA are of considerable interest because they are plausible, are generally compatible with clinical observations, and could provide a framework for hypothesis testing in human subjects. In addition, it has become clear that the traditional division of proarrhythmic effects into triggers and substrates obscures the time-dependent nature of SNSA effects. Current therapeutic approaches to counteract the proarrhythmic and other detrimental effects of SNSA are based almost solely on the use of β -adrenergic blocking drugs in a constant dose fashion. The trend has been to promote the use of longer acting continuous release formulations. Clinical trials have demonstrated the effectiveness and safety of this approach¹³² but, as discussed above, protection against VTA and sudden death is incomplete. In addition, there is still widespread underprescribing and underdosing.¹³³ The reasons for undertreatment have not been documented, however, the concern for adverse effects including cardiac decompensation, reduced exercise tolerance, bradyarrhythmias, reduced libido, etc. may be a significant factor. There is therefore a need to investigate other treatment strategies. An untested concept suggested by the temporal dependence is the use of pulsed adrenergic blockade. In patients who could not tolerate sufficiently high doses of β -blockers continuously, this might allow sufficient intensity of adrenergic block to interrupt the development of intermediate- and long-term effects and perhaps allow normal antisymphathetic mechanisms, such as enhanced vagal tone, to supervene.

Further advances will require verification of mechanisms demonstrated in animal models and their applicability to humans. The capability for

acquiring and recording physiological data preceding the onset of VTA is increasing in arrhythmia management devices, but is still largely limited to a relatively short segment of electrocardiographic waveforms. Hours of data will be needed to evaluate short- and intermediate-term SNSA influences. Another potential source of data regarding SNSA influences in human VTA is the clinical electrophysiology laboratory. It is now common practice to record electrograms from multiple epicardial and endocardial sites. With appropriate recording and signal processing techniques it is possible to obtain direct information about dispersion of repolarization as well as activation.¹³⁴ This makes it possible to test the effects of pharmacological manipulation of SNSA on spontaneous and inducible VTA analogous to the methods used in animal models. Detailed information from individual patients may provide information that improves management of the individual patient as well as better understanding of the processes that affect other patients.

REFERENCES

- Corr PB, Yamada KA, Witkowski FX. Mechanisms controlling cardiac autonomic function and their relationship to arrhythmogenesis. In Fozzard HA, Jennings RB, Haber E, Katz AM, Morgen HE (eds): *The Heart and Cardiovascular System*. Raven, NY, Scientific Foundations, 1986, pp. 1343–1403.
- Han J, Garcia de Jalon P, Moe GK. Adrenergic effects on ventricular vulnerability. *Circ Res* 1964;14:516–524.
- Maling HM, Moran NC. Ventricular arrhythmias induced by sympathomimetic amines in unanesthetized dogs following coronary occlusion. *Circ Res* 1957;5:409–413.
- Kliks BR, Burgess MJ, Abildskov JA. Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary artery occlusion. *Am J Cardiol* 1975;36:45–49.
- Kolman B, Verrier R, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle. Role of sympathetic-parasympathetic interactions. *Circulation* 1975;52:578–585.
- Butrous GS, Gough WB, Restivo M, et al. Adrenergic effects on reentrant ventricular rhythms in subacute myocardial infarction. *Circulation* 1992;86:247–254.
- Lynch JJ, Kitzen JM, Hoff PT, et al. Reduction in digitalis-associated postinfarction mortality with nadolol in conscious dogs. *Am Heart J* 1988;115:67–76.
- Dellsperger KC, Martins JB, Clothier JL, et al. Incidence of sudden cardiac death associated with coronary artery occlusion in dogs with hypertension and left ventricular hypertrophy is reduced by chronic (Beta)-adrenergic blockade. *Circulation* 1990;82:941–950.
- Hjalmarson Å, Goldstein S, Fagerberg B, et al. Effect of metoprolol CR XL in chronic heart failure: Metoprolol CR XL Randomised Intervention Trial In Congestive Heart Failure (MERIT-HF). *Lancet* 1999 Jun 19;353:2001–2007.
- Kuck KH, Cappato R, Siebels J, et al., for the CASH Investigators. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest—The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102:748–754.
- Lerman BB, Engelstein ED, Burkhoff D. Mechano-electrical feedback—Role of beta-adrenergic receptor activation in mediating load-dependent shortening of ventricular action potential and refractoriness. *Circulation* 2001 1924 Jul;104(4):486–490.
- Rump AF, Klaus W. Evidence for norepinephrine cardiotoxicity mediated by superoxide anion radicals in isolated rabbit hearts. *Naunyn Schmiedeberg's Arch Pharmacol* 1994 Mar;349(3):295–300.
- Flesch M, Maack C, Cremers B, et al. Effect of beta-blockers on free radical-induced cardiac contractile dysfunction. *Circulation* 1999 Jul 27;100(4):346–353.
- Brodde OE, Michel MC. Adrenergic and muscarinic receptors in the human heart. *Pharmacol Rev* 1999 Dec;51(4):651–690.
- Liu SJ, Kennedy RH. Alpha1-adrenergic activation of L-type Ca current in rat ventricular myocytes: Perforated patch-clamp recordings. *Am J Physiol* 1998 Jun;274(6) Part 2:H2203–H2207.
- Tseng GN, Boyden PA. Multiple types of Ca²⁺ currents in single canine Purkinje cells. *Circ Res* 1989 Dec;65(6):1735–1750.
- Apkon M, Nerbonne JM. Alpha 1-adrenergic agonists selectively suppress voltage-dependent K⁺ current in rat ventricular myocytes. *Proc Natl Acad Sci USA* 1988 Nov;85(22):8756–8760.
- Fedida D, Shimoni Y, Giles WR. Alpha-adrenergic modulation of the transient outward current in rabbit atrial myocytes. *J Physiol* 1990 Apr;423:257–277.
- Wang XL, Wettwer E, Gross G, et al. Reduction of cardiac outward currents by alpha-1 adrenoceptor stimulation: a subtype-specific effect? *J Pharmacol Exp Ther* 1991 Nov;259(2):783–788.
- Lee JH, Rosen MR. Alpha 1-adrenergic receptor modulation of repolarization in canine Purkinje fibers. *J Cardiovasc Electrophysiol* 1994 Mar;5(3):232–240.
- Lee JH, Steinberg SF, Rosen MR. A WB 4101-sensitive alpha-1 adrenergic receptor subtype modulates repolarization in canine Purkinje fibers. *J Pharmacol Exp Ther* 1991 Aug;258(2):681–687.
- Burashnikov A, Antzelevitch C. Differences in the electrophysiologic response of four canine ventricular cell types to Alpha1-adrenergic agonists. *Cardiovasc Res* 1999;43:901–908.
- Walsh KB, Kass RS. Distinct voltage-dependent regulation of a heart-delayed IK by protein kinases A and C. *Am J Physiol* 1991 Dec;261(6) Part 1:C1081–C1090.
- Tohse N, Nakaya H, Kanno M. Alpha 1-adrenoceptor stimulation enhances the delayed rectifier K⁺ current of guinea pig ventricular cells through the activation of protein kinase C. *Circ Res* 1992 Dec;71(6):1441–1446.
- Fedida D, Braun AP, Giles WR. Alpha 1-adrenoceptors in myocardium: functional aspects and transmembrane signaling mechanisms. *Physiol Rev* 1993 Apr;73(2):469–487.
- Shah A, Cohen IS, Rosen MR. Stimulation of cardiac alpha receptors increases Na/K pump current and decreases gK via a pertussis toxin-sensitive pathway. *Biophys J* 1988 Aug;54(2):219–225.
- Koumi S, Backer CL, Arentzen CE, et al. Beta-adrenergic modulation of the inwardly rectifying potassium channel in isolated human ventricular myocytes. Alteration in channel response to beta-adrenergic stimulation in failing human hearts. *J Clin Invest* 1995 Dec;96(6):2870–2881.

28. Parker JD, Newton GE, Landzberg JS, et al. Functional significance of presynaptic alpha-adrenergic receptors in failing and nonfailing human left ventricle. *Circulation* 1995 Oct;92(7):1793-1800.
29. Walsh DA, Van Patten SM. Multiple pathway signal transduction by the cAMP-dependent protein kinase. *FASEB J* 1994 Dec;8(15):1227-1236.
30. Kaumann AJ, Molenaar P. Modulation of human cardiac function through 4 beta-adrenoceptor populations. *Naunyn Schmiedeberg Arch Pharmacol* 1997 Jun;355(6):667-681.
31. Zygmunt AC. Intracellular calcium activates chloride current in canine ventricular myocytes. *Am J Physiol* 1994;267:H1984-H1995.
32. Gaughan JP, Hefner CA, Houser SR. Electrophysiological properties of neonatal rat ventricular myocytes with alpha1-adrenergic-induced hypertrophy. *Am J Physiol* 1998 Aug;275(2) Part 2:H577-H590.
33. Levy MN. Sympathetic-parasympathetic interactions in the heart. In Kulbertus HE, Frank G (eds): *Neurocardiology*. Mt Kisco, NY, Futura Publishing Co., 1988, pp. 85-98.
34. Reid DS, Tynan M, Braidwood L, et al. Bidirectional tachycardia in a child. A study using His bundle electrography. *Br Heart J* 1975;37:339-344.
35. Coumel P, Fidelle J, Lucet V, et al. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. *Br Heart J* 1978;40(Suppl.):28-37.
36. Swan H, Laitinen PJ. Familial polymorphic ventricular tachycardia—intracellular calcium channel disorder. *Cardiac Electrophysiol Rev* 2002;6:81-87.
37. Coumel P. Catecholaminergic polymorphic ventricular tachyarrhythmias in children. *Cardiac Electrophysiol Rev* 2002;6:93-95.
38. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children: A 7-year follow-up of 21 patients. *Circulation* 1995;91:1512-1519.
39. Wellens HJJ. The electrocardiogram in digitalis intoxication. In Yu PN, Goodwin JF (eds): *Progress in Cardiology*. Philadelphia, Lea & Febiger, 1976, pp. 271-290.
40. Rosen MR, Danilo P Jr. Effects of tetrodotoxin, lidocaine, verapamil and AHR-2666 on ouabain-induced delayed after depolarizations in canine Purkinje fibers. *Circ Res* 1980;46:117-124.
41. Priori SG, Mantica M, Schwartz PJ. Delayed afterdepolarizations elicited in vivo by left stellate ganglion stimulation. *Circulation* 1988;78:178-185.
42. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. *Am J Physiol* 1990;258:H1796-H1805.
43. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;103:196-200.
44. Laitinen PJ, Brown KM, Piippo K, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001;103:485-490.
45. Marx SO, Reiken S, Hisamatsu Y, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): Defective regulation in failing hearts. *Cell* 2000;101:365-376.
46. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000 Feb;101:616-623.
47. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N Engl J Med* 1971;285:903-904.
48. Hoffman BF, Cranefield PF. *Electrophysiology of the heart*. New York, McGraw-Hill, 1960.
49. Ali RHH, Zareba W, Moss AJ, et al. Clinical and genetic variables associated with acute arousal and nonarousal-related cardiac events among subjects with the long QT syndrome. *Am J Cardiol* 2000 Feb;85:457-461.
50. Schwartz PJ, Malteo PS, Moss AJ, et al. Gene-specific influence on the triggers for cardiac arrest in the long QT syndrome (abstr). *Circulation* 1997;96:1-212.
51. Wilde AAM, Jongbloed RJE, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J Am Coll Cardiol* 1999;33:327-332.
52. Moss AJ, Robinson JL, Gessman L, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *Am J Cardiol* 1999;84:876-879.
53. Stramba-Badiale M, Priori SG, Napolitano C, et al. Gene-specific differences in the circadian variation of ventricular repolarization in the long QT syndrome: A key to sudden death during sleep? *Ital Heart J* 2000;1:323-328.
54. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 2000;35:778-786.
55. Priori SG, Napolitano C, Cantu F, et al. Differential response to Na⁺ channel blockade, beta-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. *Circ Res* 1996 Jun;78(6):1009-1015.
56. Volders PGA, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K⁺ currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. *Circulation* 1999;100:2455-2461.
57. Cao JM, Fishbein MC, Han JB, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* 2000;101:1960-1969.
58. Yoshioka K, Gao DW, Chin M, et al. Heterogeneous sympathetic innervation influences local myocardial repolarization in normally perfused rabbit hearts. *Circulation* 2000 Mar;101:1060-1066.
59. Bryant SM, Shipsey SJ, Hart G. Normal regional distribution of membrane current density in rat left ventricle is altered in catecholamine-induced hypertrophy. *Cardiovasc Res* 1999;42:391-401.
60. Yao JA, Jiang M, Fan JS, et al. Heterogeneous changes in K currents in rat ventricles three days after myocardial infarction. *Cardiovasc Res* 1999;44:132-145.
61. Anderson KP, Walker R, Dustman T, et al. Spontaneous sustained ventricular tachycardia in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial. *J Am Coll Cardiol* 1995;26:489-496.
62. de Bakker AMT, Coronel R, Tasseron S, et al. Ventricular tachycardia in the infarcted Langendorff-perfused human heart: Role of the arrangement of surviving cardiac fibers. *J Am Coll Cardiol* 1990;15:1594-1607.
63. Anderson KP, Walker R, Urie P, et al. Myocardial electrical propagation in patients with idiopathic dilated cardiomyopathy. *J Clin Invest* 1993;92:122-140.
64. Spach MS, Dolber PC, Heidlage JF. Influence of the passive anisotropic properties on directional differences in propagation following modification of the sodium conductance in human atrial muscle: A model of reentry based on anisotropic discontinuous propagation. *Circ Res* 1988;62:811-832.
65. Lesh MD, Pring M, Spear JF. Cellular uncoupling can unmask dispersion of action potential duration in ventricular myocardium. *Circ Res* 1989;65:1426-1440.

66. Anderson KP. Sudden death, hypertension and hypertrophy. *J Cardiovasc Pharmacol* 1984;6:S498-S503.
67. Cohn JN, Levine B, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-823.
68. Meredith IT, Broughton A, Jennings GL, et al. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 1991;325:618-624.
69. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807-2816.
70. Schenk EA, Moss AJ. Cardiovascular effects of sustained norepinephrine infusions. II. Morphology. *Circ Res* 1966 May;18(5):605-615.
71. Bisognano JD, Weinberger HD, Bohlmeier TJ, et al. Myocardial-directed overexpression of the human beta(1)-adrenergic receptor in transgenic mice. *J Mol Cell Cardiol* 2000 May;32(5):817-830.
72. Engelhardt S, Hein L, Wiesmann F, et al. Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. *Proc Natl Acad Sci USA* 1999 Jun;96(12):7059-7064.
73. Liggett SB, Tepe NM, Lorenz JN, et al. Early and delayed consequences of beta2-adrenergic receptor overexpression in mouse hearts: Critical role for expression level. *Circulation* 2000 Apr;101:1707-1714.
74. Lemire I, Ducharme A, Tardif JC, et al. Cardiac-directed overexpression of wild-type alpha1B-adrenergic receptor induces dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2001 Aug;281(2):H931-H938.
75. Iwase M, Bishop SP, Uechi M, et al. Adverse effects of chronic endogenous sympathetic drive induced by cardiac GS alpha overexpression. *Circ Res* 1996 Apr;78(4):517-524.
76. Geng YJ, Ishikawa Y, Vatner DE, et al. Apoptosis of cardiac myocytes in Gsalpha transgenic mice. *Circ Res* 1999 Jan;84(1):34-42.
77. Vatner DE, Yang GP, Geng YJ, et al. Determinants of the cardiomyopathic phenotype in chimeric mice overexpressing cardiac Gsalpha. *Circ Res* 2000 Apr;86(7):802-806.
78. Asai K, Yang GP, Geng YJ, et al. Beta-adrenergic receptor blockade arrests myocyte damage and preserves cardiac function in the transgenic G(salpha) mouse. *J Clin Invest* 1999 Sep;104(5):551-558.
79. Hassankhani A, Steinhilber ME, Soonpaa MH, et al. Overexpression of NGF within the heart of transgenic mice causes hyperinnervation, cardiac enlargement, and hyperplasia of ectopic cells. *Dev Biol* 1995 May;169(1):309-321.
80. Heath BM, Xia J, Dong E, et al. Overexpression of nerve growth factor in the heart alters ion channel activity and beta-adrenergic signalling in an adult transgenic mouse. *J Physiol* 1998 Nov;512 Part 3:779-791.
81. Saito S, Hiroi Y, Zou Y, et al. Beta-adrenergic pathway induces apoptosis through calcineurin activation in cardiac myocytes. *J Biol Chem* 2000 Nov;275(44):34528-34533.
82. Communal C, Singh K, Sawyer DB, et al. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: Role of a pertussis toxin-sensitive G protein. *Circulation* 1999 Nov;100(22):2210-2212.
83. Port JD, Bristow MR. Altered beta-adrenergic receptor gene regulation and signaling in chronic heart failure. *J Mol Cell Cardiol* 2001 May;33(5):887-905.
84. Morisco C, Zebrowski DC, Vatner DE, et al. Beta-adrenergic cardiac hypertrophy is mediated primarily by the beta(1)-subtype in the rat heart. *J Mol Cell Cardiol* 2001 Mar;33(3):561-573.
85. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol* 1995 Apr;25(5):1154-1161.
86. Lowes BD, Gill EA, Abraham WT, et al. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. *Am J Cardiol* 1999 Apr;83(8):1201-1205.
87. Leclercq JF, Maison-Blanche P, Cauchemez B, et al. Respective role of sympathetic tone and of cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holter monitoring. *Eur Heart J* 1988;9:1276-1283.
88. Shusterman V, Aysin B, Gottipaty V, et al. for the ESVM Investigators. Autonomic nervous system activity and the spontaneous initiation of ventricular tachycardia. *J Am Coll Cardiol* 1998;33:1891-1899.
89. Anderson KP, Lux RL, Dustman T. Comparison of QRS morphologies of spontaneous premature ventricular complexes and ventricular tachycardia induced by programmed stimulation. *Am Heart J* 1990;119(6):1302-1311.
90. Anderson KP, Shusterman V, Aysin B, for the ESVM Investigators. Distinctive RR dynamics preceding two modes of onset of spontaneous sustained ventricular tachycardia. *J Cardiovasc Electrophysiol* 1999;10:897-904.
91. Shusterman V, Aysin B, Anderson KP, et al. Multidimensional rhythm disturbances as a precursor of sustained ventricular tachyarrhythmias. *Circ Res* 2001 Apr;88(7):705-712.
92. Pak PH, Nuss HB, Tunin RS, et al. Repolarization abnormalities, arrhythmia and sudden death in canine tachycardia-induced cardiomyopathy. *J Am Coll Cardiol* 1997 Aug;30(2):576-84.
93. Nábauer M, Beuckelmann DJ, Überfuhr P, et al. Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. *Circulation* 1996 Jan;93(1):168-177.
94. Aimond F, Alvarez JL, Rauzier JM, et al. Ionic basis of ventricular arrhythmias in remodeled rat heart during long-term myocardial infarction. *Cardiovasc Res* 1999;42:402-415.
95. Dixon JE, Shi W, Wang HS, et al. Role of the Kv4.3 K⁺ channel in ventricular muscle. A molecular correlate for the transient outward current. *Circ Res* 1996 Oct;79(4):659-668.
96. Zhang TT, Takimoto K, Stewart AFR, et al. Independent regulation of cardiac Kv4.3 potassium channel expression by angiotensin II and phenylephrine. *Circ Res* 2001 Mar;88(5):476-482.
97. Pogwizd SM, Schlotthauer K, Li L, et al. Arrhythmogenesis and contractile dysfunction in heart failure—Roles of sodium-calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. *Circ Res* 2001 Jun;88(11):1159-1167.
98. Pogwizd SM. Nonreentrant mechanisms underlying spontaneous ventricular arrhythmias in a model of nonischemic heart failure in rabbits. *Circulation* 1995 Aug;92(4):1034-1048.
99. Satoh N, Suter TM, Liao R, et al. Chronic alpha-adrenergic receptor stimulation modulates the contractile phenotype of cardiac myocytes in vitro. *Circulation* 2000 Oct;102(18):2249-2254.
100. Koumi S, Backer CL, Arentzen CE. Characterization of inwardly rectifying K⁺ channel in human cardiac myocytes. Alterations in channel behavior in myocytes isolated from

- patients with idiopathic dilated cardiomyopathy. *Circulation* 1995 Jul;92(2):164-174.
101. Kaabs, Nuss HB, Chiamvimonvat N, et al. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. *Circ Res* 1996 Feb;78(2):262-273.
 102. Lopatin AN, Nichols CG. Inward rectifiers in the heart: an update on I(K1). *J Mol Cell Cardiol* 2001 Apr;33(4):625-638.
 103. Du XJ, Dart AM. Role of sympathoadrenergic mechanisms in arrhythmogenesis. *Cardiovasc Res* 1999;43:832-834.
 104. Chen PS, Chen LS, Cao JM, et al. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res* 2001 May;50(2):409-416.
 105. Cao JM, Chen LS, KenKnight BH, et al. Nerve sprouting and sudden cardiac death. *Circ Res* 2000 Apr;86(7):816-821.
 106. Zhou S, Cao JM, Tebb ZD, et al. Nerve sprouting and sudden cardiac death. *J Cardiovasc Electrophysiol* 2001;12:1068-1073.
 107. Pinto JM, Boyden PA. Electrical remodeling in ischemia and infarction. *Cardiovasc Res* 1999 May;42(2):284-297.
 108. Yanowitz F, Preson JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles. *Circ Res* 1966;18:416-428.
 109. Schwartz PJ, Verrier RL, Lown B. Effect of stellectomy and vagotomy on ventricular refractoriness in dogs. *Circ Res* 1977 Jun;40(6):536-540.
 110. Vos MA, De Groot SHM, Verduyn SC, et al. Enhanced susceptibility for acquired torsade de pointes arrhythmias in the dog with chronic, complete AV block is related to cardiac hypertrophy and electrical remodeling. *Circulation* 1998 Sep;98:1125-1135.
 111. Pagani M, Montano N, Porta A, et al. The relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 1997;95:1441-1448.
 112. Van de Borne P, Montano N, Zimmerman B, et al. Relationship between repeated measures of hemodynamics, muscle sympathetic nerve activity, and their spectral oscillations. *Circulation* 1997 Dec;96:4326-4332.
 113. Shusterman V, Anderson KP, Barnea O. Spontaneous skin temperature oscillations in normal human subjects. *Am J Physiol (Regulatory, Integrative, Comp Physiol)* 1997;42:R1173-R1181.
 114. Akselrod S, Gordon D, Ubel FA, et al. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213:220-222.
 115. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043-1065.
 116. Eckberg DL. Sympathovagal balance: a critical appraisal. *Circulation* 1997 Nov;96(9):3224-3232.
 117. Cooley RL, Montano N, Cogliati C, et al. Evidence for a central origin of the low-frequency oscillation in RR-interval variability. *Circulation* 1998 Aug;98(6):556-561.
 118. van de Borne P, Montano N, Pagani M, et al. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation* 1997;95:1449-1954.
 119. Guzzetti S, Cogliati C, Turiel M, et al. Sympathetic predominance followed by functional denervation in the progression of chronic heart failure. *Eur Heart J* 1995;16:1100-1107.
 120. Bigger JT, Fleiss JL, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164-171.
 121. Moguilevski V, Oliver J, McGrath BP. Sympathetic regulation in rabbits with heart failure: Experience using power spectral analysis of heart rate variability. *Clin Exp Pharmacol Physiol* 1995;22:475-477.
 122. Shusterman V, Aysin B, Weiss R, et al. for the ESVM Investigators. Dynamics of low-frequency R-R interval oscillations preceding spontaneous ventricular tachycardia. *Am Heart J* 2000;139:126-133.
 123. Levy MN, Martin PJ. Autonomic neural control of cardiac function. In Sperelakis N (ed): *Physiology and Pathophysiology of the Heart*, 3rd Edition, Boston, MA, Kluwer Academic Publishers, 1995, pp. 413-430.
 124. Yang T, Levy MN. Sequence of excitation as a factor in sympathetic-parasympathetic interactions in the heart. *Circ Res* 1992;71:898-905.
 125. Yang T, Levy MN. Effects of intense antecedent sympathetic stimulation on sympathetic neurotransmission in the heart. *Circ Res* 1993;72:137-44.
 126. Yang T, Senturia JB, Levy MN. Antecedent sympathetic stimulation alters time course of chronotropic response to vagal stimulation in dogs. *Am J Physiol* 1994 Apr;266(4) Part 2:H1339-H1347.
 127. Eckberg DI, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877-883.
 128. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and β -adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;307:205-211.
 129. Rundqvist B, Eisenhofer G, Elam M, et al. Attenuated cardiac sympathetic responsiveness during dynamic exercise in patients with heart failure. *Circulation* 1997 Feb;95:940-945.
 130. Olivari MT, Levine TB, Cohn JN. Abnormal neurohumoral response to nitroprusside infusion in congestive heart failure. *J Am Coll Cardiol* 1983;2:411-417.
 131. Communal C, Singh K, Sawyer DB, et al. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: Role of a pertussis toxin-sensitive G protein. *Circulation* 1999 Nov;100(22):2210-2212.
 132. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure—A Bayesian meta-analysis. *Ann Intern Med* 2001;134:550-560.
 133. Krumholz HM, Radford MJ, Wang Y, et al. National use and effectiveness of Beta-blockers for the treatment of elderly patients after acute myocardial infarction—National cooperative cardiovascular project. *JAMA* 1998;280:623-629.
 134. Anderson KP, Walker R, Dustman T, et al. Rate-related electrophysiologic effects of long-term amiodarone administration on canine ventricular myocardium in vivo. *Circulation* 1989;79:948-958.