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AUTONOMIC ASPECTS OF ARRHYTHMOGENESIS: THE ENDURING AND THE NEW

Richard L. Verrier, Ph.D.¹ and Charles Antzelevitch, Ph.D.²

¹*From: Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA and*

²*Masonic Medical Research Laboratory, Utica, NY.*

Abstract

Recent progress in our understanding of the role of the autonomic nervous system in the development of cardiac arrhythmias is reviewed. Our focus is on the translation of basic principles of neural control of heart rhythm that have emerged from experimental studies to clinical applications. Recent studies have made significant strides in defining the function of intrinsic cardiac innervation and the importance of nerve sprouting in electrical remodeling. A recurring theme is that heterogeneity of sympathetic innervation in response to injury is highly arrhythmogenic. In addition, both sympathetic and parasympathetic influences on ion channel activity have been found accentuate electrical heterogeneities and thus to contribute to arrhythmogenesis in the long QT and Brugada syndromes. In the clinic, heart rate variability continues to be a useful tool in delineating pathophysiologic changes that result from the progression of heart disease and the impact of diabetic neuropathy. Heart rate turbulence, a noninvasive indicator of baroreceptor sensitivity has emerged as a simple, practical tool to assess risk for cardiovascular mortality in patients with ischemic heart disease and heart failure. Evidence of the proarrhythmic influence of behavioral stress has been further bolstered by defibrillator discharge studies and ambulatory ECG-based T-wave alternans measurement. In summary, the results of recent investigations underscore the importance of the autonomic influences as triggers of arrhythmia and provide important mechanistic insights into the ionic and cellular mechanisms involved.

Keywords

cardiac arrhythmias; LQTS; Brugada syndrome; baroreceptor reflexes; electrical remodeling; intrinsic cardiac innervation; behavioral stress

Introduction

The concept that neural activity exerts a potent influence on arrhythmogenesis was highlighted in the 1970's¹ and has continued to receive affirmation in contemporary literature. An intriguing aspect of the evolving research has been the divergence of lines of investigations. Whereas some principles have been studied primarily in the clinical domain, exploration of other facets has progressed primarily at the molecular and genetic levels. For example, study of autonomic tone and baroreceptor function has been pursued primarily in clinical studies aimed at characterizing disease states and achieving sudden death risk stratification. The long QT and Brugada syndromes have provided the inspiration for experimental studies to define the

Correspondence to: Charles Antzelevitch, Ph.D., Executive Director and Director of Research, Gordon Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker St., Utica NY 13501-1787, Phone: 315-735-2217 x117, FAX: 315-735-5648, Email: ca@mmrl.edu. Supported by Grants R01 HL63968 (RLV) HL 47678 (CA) from the National Heart, Lung, and Blood Institute of the National Institutes of Health, the American Heart Association, New York State Affiliate (CA) and the Masons of New York State and Florida.

genetic, molecular, ionic and cellular mechanism responsible for changes in cardiac vulnerability.

Integration of Neural Control of Cardiac Electrical Activity

Regulation of cardiac neural activity is highly integrated and is achieved by circuitry at multiple levels² (Fig. 1). Higher brain centers operate through elaborate pathways within the hypothalamus and medullary cardiovascular regulatory sites. Baroreceptor mechanisms have long been recognized as integral to autonomic control of the cardiovascular system, and significant clinical applications of this knowledge have been realized through heart rate variability and baroreceptor sensitivity testing. The intrinsic cardiac nerves and fat pads appear to provide local neural coordination independent of higher brain centers. Newly recognized is the phenomenon of electrical remodeling attributable to nerve growth and degeneration. At the level of the myocardial cell, considerable progress has been made to define the intimate role of the autonomic receptors as they influence G proteins to control ionic channels, pumps, and exchangers. Finally, studies of behavioral state provide evidence that markers of arrhythmia vulnerability can be monitored during emotional and physical stressors and sleep states to identify individuals at heightened risk of lethal cardiac arrhythmias.

Autonomic Nervous System Tone and Reflexes

Heart Rate Variability (HRV)

Autonomic nervous system tone has been studied primarily in human subjects by employing the tool of HRV, which relies on the principle that the pattern of beat-to-beat control of the sinoatrial (SA) node provides a reflection of autonomic activity. The physiological basis for HRV analysis stems from the fact that parasympathetic influences exert a unique imprimatur through rapid dynamic control by acetylcholine affecting muscarinic receptors and are therefore reflected in the high-frequency (HF) component of HRV. Sympathetic nerve activity, through the influence of norepinephrine on beta-adrenergic receptors, has a considerably slower influence and is manifest in the lower frequency (LF) components. Thus, HRV is only an indirect measure of autonomic function as it reflects influences on the SA node and not on the ventricular myocardium. Nevertheless, it provides basic insights into general autonomic changes associated with disease states.

A number of recent studies have focused on the use of heart rate variability to define autonomic status in patients with coronary artery disease³, cardiomyopathy⁴, moderately elevated blood pressure⁵, diabetes, in cardiac surgery patients⁶, in normal ageing⁷, and its improvement with exercise conditioning⁸. In diabetic patients, HRV has been used to identify patients with incipient disease^{9–11} and to indicate mechanisms that underlie the development or severity of the disease, including mitochondrial DNA mutation¹², peptide status¹³, or suppression of uric acid¹⁴. Excellent commentaries have appeared recently^{3,15}. Routledge and colleagues¹⁶ developed the case that HRV may serve as a potential therapeutic guide, citing its improvement by exercise. Indeed, the benefits of physical activity (self-reported walking duration and pace) in men with type 2 diabetes include reduced risk of cardiovascular disease, cardiovascular death, and total mortality¹⁷. Conflicting results have been found regarding association of autonomic balance as assessed by HRV with cardiovascular disease¹⁸ and lethal arrhythmias¹⁹.

Among the frontiers of HRV application is analysis of the autonomic effects of air particulate pollution^{20,21} to investigate the causes of increased cardiorespiratory morbidity and mortality associated with periods of poor air quality.

Baroreceptor Sensitivity

The classic studies by Billman, Schwartz and Stone²² drew attention to the importance of baroreceptor function in susceptibility to life-threatening arrhythmias associated with myocardial ischemia and infarction. In their initial investigations in canines, they demonstrated that the more powerful was the baroreflex response, the less vulnerable animals were to ventricular fibrillation during myocardial ischemia superimposed on prior myocardial infarction. The protective effect of the baroreceptor mechanism has been linked primarily to the antibrillatory influence of vagus nerve activity, which presynaptically inhibits norepinephrine release²³ and maintains heart rate low during myocardial ischemia²⁴. The latter effect improves diastolic coronary perfusion, minimizing the ischemic insult from coronary artery occlusion. The importance of baroreceptor sensitivity (BRS) was subsequently documented in human subjects in whom baroreceptor function was evaluated with the pressor agent phenylephrine. LaRovere and colleagues²⁵ demonstrated that patients who experienced a myocardial infarction were less likely to experience sudden cardiac death if their baroreceptor function was not depressed.

In the last few years, exploration of BRS has been pursued using the tool of heart rate turbulence (HRT), which refers to fluctuations of sinus-rhythm cycle length after a single ventricular premature beat (VPB) and appears to be mechanistically linked with BRS²⁶. The basic principle, introduced by Schmidt and coworkers²⁷, is that the reaction of the cardiovascular system to a VPB and subsequent decrease in arterial blood pressure is a direct function of baroreceptor responsiveness as reflex activation of the vagus nerve controls the pattern of sinus rhythm. Several studies confirm that in low-risk patients, after a VPB, sinus rhythm exhibits a characteristic pattern of early acceleration and subsequent deceleration. By contrast, patients at high-risk exhibit essentially a flat, nonvarying response to the VPB, indicating inability to activate vagal nerves and their cardioprotective effect^{28;29}. The method appears to be a promising independent predictor of total mortality, in patients with ischemic heart disease and/or heart failure^{30–32}.

HRT has the intrinsic advantages of being an inexpensive, simple method that can be analyzed from routine ambulatory ECGs. Its main shortcoming is its requirement of spontaneous, single VPBs, without which the analysis cannot be performed for AECGs. In the electrophysiology laboratory, induction of premature beats allows HRT measurement in individuals with few premature beats³³.

Intrinsic Cardiac Innervation

In the late 1970's, Armour³⁴ and his colleagues introduced and investigated the elaborate intrinsic neural network within the heart that provides local, independent heart rhythm control. This important advance was subsequently verified by Randall, Zipes, and their respective coworkers^{35;36}, who drew attention to the fact that components of this innervation system reside within discrete fat pads. The cardiac fat pads and local cardiac regulatory systems, although somewhat enigmatic in their regulatory function, are of considerable clinical significance³⁷. For example, myocardial ischemia can compromise the functional capacity of cardiac intrinsic neurons residing in the fat pad and thus has the potential to increase electrical inhomogeneity and susceptibility to arrhythmias³⁸. Intrinsic innervation is also vulnerable to diabetic neuropathy, which accordingly could exacerbate vulnerability to arrhythmias³⁹. Surgical incisions through the atrial walls and radiofrequency ablation may isolate SA node pacemaker cells and damage the fat pads and result in proarrhythmia due to iatrogenically induced autonomic imbalance⁴⁰. Recently, Nakajima and colleagues⁴¹ provided evidence in canine hearts that heterogeneity of fibers within and without the fat pads contributes to dispersion of electrical activity, which in turn can predispose to arrhythmogenesis in adjacent atrial tissue. Contemporaneous analyses in cardiac surgery patients verified that an epicardial

fat pad located near the junction of the left atrium and right inferior pulmonary vein contains parasympathetic nerve fibers that selectively innervate the atrioventricular but not the sinoatrial node⁴².

Nerve Growth and Degeneration

Whereas the concept of remodeling has been well established with respect to the heart, the importance of restructuring of cardiac innervation has not received due attention until the past few years. Fundamental contributions in this regard have emerged from the laboratories of Zipes^{43;44} and Chen^{45–48}. In particular, Jayachandran et al⁴⁴ demonstrated in a canine model of atrial fibrillation induced by rapid, prolonged pacing, that atrial electrical remodeling was associated with spatially heterogeneous uptake of the postganglionic sympathetic indicator hydroxyephedrine into the nerve terminals within the sinus node, crista terminalis, and myocardium. Importantly, increased uptake was accompanied by electrical heterogeneity and augmented norepinephrine tissue levels. Subsequent studies by Chang⁴⁵ and Olgin⁴⁴ and their respective colleagues provided further evidence in favor of the concept of injury-induced neural repair with selective sympathetic remodeling and the attendant potential for induction and perpetuation of atrial arrhythmias. Chen and coworkers⁴⁶ provided groundbreaking evidence that nerve sprouting could apply to ventricular arrhythmogenesis and potentially sudden cardiac death. These investigators demonstrated a significant correlation between increased sympathetic nerve density as reflected in immunocytochemical markers and history of ischemia in native hearts of human transplant recipients. In a canine model, they demonstrated cogently that induction of nerve sprouting with nerve growth factor resulted in increased incidence of ventricular tachycardias and sudden death, with concomitant presence of T-wave alternans, a noninvasive marker of risk for ventricular arrhythmias⁴⁸. Significantly, the predisposition to arrhythmias was linked to immunocytochemical evidence of a heterogeneous pattern of sympathetic nerve reinnervation. Recently, Liu and coworkers⁴⁹ demonstrated in rabbits that hypercholesterolemia can produce proarrhythmic neural and electrophysiological remodeling that is highly arrhythmogenic and is associated with important changes in ionic currents including I_{Ca} . Collectively, this evidence points to the lability of autonomic innervation and the intricate changes that may be responsible for derangements in neural activity and predisposition to arrhythmias. This adverse effect of heterogeneous remodeling of sympathetic innervation to the heart is likely to play a role in the increased risk for life-threatening arrhythmias.

Autonomic-mediated accentuation of spatial dispersion of repolarization

Electrical heterogeneities of ventricular repolarization are responsible for the inscription of the J wave and T wave of the ECG.⁵⁰ Amplification of these heterogeneities contribute to the electrocardiographic phenotype and arrhythmogenicity of channelopathies such as the Brugada and long QT syndromes and autonomic influences play a prominent role in unmasking these syndromes and precipitating lethal events.⁵⁰

Brugada Syndrome—Initially described as a new clinical entity in 1992,⁵¹ the Brugada syndrome is characterized by 1) an accentuated ST segment elevation or J wave appearing principally in the right precordial leads (V1–V3), often followed by a negative T wave; 2) very closely coupled extrasystoles; and 3) rapid polymorphic VT, which at times may be indistinguishable from VF. The ECG sign of the Brugada syndrome is dynamic and often concealed, but can be unmasked by potent sodium channel blockers such as ajmaline, flecainide, procainamide, disopyramide, propafenone and pilsicainide^{52–54}. In addition to sodium channel blockers, a febrile state, vagotonic agents, α adrenergic agonists, β adrenergic blockers, tricyclic antidepressants, first generation antihistaminics (dimenhydrinate), alcohol

intoxication, insulin+glucose, and cocaine toxicity can unmask the Brugada syndrome or lead to accentuation of ST segment elevation in patients with the syndrome.^{52,55-62}

The arrhythmogenic substrate responsible for the development of extrasystoles and polymorphic VT in the Brugada syndrome is thought to develop as a result of a rebalancing of currents active at the end of phase 1, leading to accentuation of the right ventricular action potential notch, eventually leading to loss of the action potential dome at some right ventricular epicardial sites but not others. Transmural and epicardial dispersion of repolarization is the result. The transmural dispersion underlies ST Segment elevation and the development of a vulnerable window across the ventricular wall, whereas the epicardial dispersion of repolarization facilitates the development of phase 2 reentry, which generates a phase 2 reentrant extrasystole that captures the vulnerable window to precipitate VT/VF in the form of reentry. Vagotonic agents and maneuvers, α adrenergic agonists, and β adrenergic blockers facilitate this process by reducing inward calcium current, thus causing an outward shift in the current flowing during phase 1 of the action potential. Vagotonic agents may also contribute by augmenting outward potassium currents.

Recent studies have demonstrated reduced regional uptake of the norepinephrine analogue [123I]m-iodobenzylguanidine (123I-MIBG) in 8 (47%) of 17 patients with Brugada syndrome but not in control subjects.³¹ Segmental reduction of 123I-MIBG uptake was observed in the inferior and septal left ventricular wall pointing to presynaptic sympathetic dysfunction of the heart in a large fraction of patients with Brugada syndrome. The pathophysiological implication of this finding remains to be delineated.

Long QT Syndrome (LQTS)—The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the ECG, a atypical polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), and a high risk for sudden cardiac death.⁶³⁻⁶⁵ Congenital LQTS is generally subdivided into seven genotypes distinguished by mutations in at least six different ion genes and an structural anchoring protein located on chromosomes 3, 4, 7, 11, 17 and 21.⁶⁶⁻⁷¹ Acquired LQTS refers to a syndrome similar to the congenital form but caused by exposure to drugs that prolong the duration of the ventricular action potential,⁷² or QT prolongation secondary to bradycardia or an electrolyte imbalance. In recent years this syndrome has been extended to encompass the reduced repolarization reserve attending remodeling of the ventricular myocardium that accompanies dilated and hypertrophic cardiomyopathies.⁷³⁻⁷⁷

Here again, amplification of spatial dispersion of repolarization within the ventricular myocardium is thought to generate the principal arrhythmogenic substrate. The accentuation of spatial dispersion is typically secondary to an increase of transmural and trans-septal dispersion of repolarization and the development of early after depolarization (EAD)-induced triggered activity underlie the substrate and trigger for the development of Torsade de Pointes arrhythmias observed under LQTS conditions (Figure 4).^{50,78,79} Experimental models of the LQT1, LQT2, and LQT3 forms of the long QT syndrome have been developed using the canine arterially perfused left ventricular wedge preparation (Figure 4)⁸⁰. These models have provided us insights into the cellular mechanisms responsible for the development of life-threatening Torsade de Pointes arrhythmias and the mechanism by which sympathetic stimuli precipitate lethal events. In LQT1, 2 and 3 experimental models, preferential prolongation of the M cell APD leads to an increase in the QT interval as well as an increase in transmural dispersion of repolarization (TDR), the latter providing the substrate for the development of spontaneous as well as stimulation-induced Torsade de Pointes (TdP).

LQT1, the most prevalent of the congenital long QT syndromes,⁸¹ is characterized by loss of function of the slowly activating delayed rectifier (IKs). The syndrome can be mimicked in

the perfused wedge preparation using an IKs blocker (chromanol 293B) together with a β -adrenergic agonist (isoproterenol). Chromanol 293B alone leads to uniform prolongation of APD in all three cell types with little change in TDR. Although the QT interval is prolonged, TdP never occurs under these conditions, nor can it be induced. Addition of isoproterenol results in abbreviation of epicardial and endocardial APD while the M cell APD either prolongs or remains the same. The dramatic increase in TDR provides the substrate for the development of spontaneous as well as stimulation-induced TdP⁸². These findings are consistent with the high sensitivity of congenital LQTS patients, especially LQT1 patients, to sympathetic stimulation^{63;83}. The results also support the hypothesis that the problem with the long QT syndrome is not the long QT interval, but rather the increase in TDR that often accompanies prolongation of the QT interval.

LQT2, the second most prevalent form of congenital LQTS, and most forms of drug-induced acquired LQTS, are characterized by loss of function of the rapidly activating delayed rectifier current (IKr). The IKr blocker, D-sotalol has been used to mimic LQT2. Although all three cell types exhibit an increase in APD when IKr is blocked, the M cell prolongs to a greater degree, resulting in accentuation of TDR and spontaneous as well as stimulation-induced TdP. Isoproterenol further exaggerates TDR and increases the incidence of TdP in this model.

LQT3 is far less common and is due to gain in function of the late sodium current (late INa). ATX-II, a sea anemone toxin that augments late INa, is used to mimic this form of the disease. The APD of each of the three cell types is prolonged, leading to a delay in the onset of the T wave⁸⁴. As in the other forms of LQTS, preferential prolongation of APD in the M region results in an increase in TDR and induction of TdP. β adrenergic stimulation abbreviates APD of all cell types under these conditions, causing an ameliorative effect in this model of LQTS. TDR is importantly reduced owing to a greater abbreviation of the APD of the M cell⁸⁵.

The response to sympathetic activation displays a very different time-course in the case of LQT1 and LQT2, both in experimental models (Fig. 4) and in the clinic^{78;86;87}. In LQT1, β adrenergic stimulation induces an increase in TDR that is most prominent during the first two minutes, but which persists, although to a lesser extent, during steady-state. TdP incidence is enhanced during the initial period as well as during steady-state. In LQT2, isoproterenol produces only a transient increase in TDR that persists for less than 2 minutes. TdP incidence is therefore enhanced only for a brief period of time. These differences in time-course may explain the important differences in autonomic activity and other gene-specific triggers that contribute to events in patients with different LQTS genotypes^{81;83;87}.

While β blockers are considered the first line of therapy in patients with LQT1, they have not been shown to be beneficial in LQT3. Preliminary data suggest LQT3 patients might benefit from Na⁺ channel blockers, such as mexiletine and flecainide but long-term data are not yet available.^{88;89} Experimental data have shown that mexiletine reduces transmural dispersion and prevents TdP in LQT3 as well as LQT1 and LQT2, suggesting that agents that block the late sodium current may be effective in all forms of LQTS.^{82;84} These observations suggest that a combination of β blockers and late sodium channel blockers may confere more protection in LQT1 and LQT2 than β blockade alone. Clinical data are not available as yet.

Behavioral State

The view that behavioral factors may predispose to malignant arrhythmias has gained strong support in recent years because of batteries of psychometric tests for behavioral testing and indicators of cardiac electrical instability including defibrillator discharge frequency and T-wave alternans (TWA).

Recently, Lampert and colleagues⁹⁰ systematically examined the linkage between emotional and physical stressors in provoking spontaneous ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICDs). Detailed diaries of mood states and physical activity were obtained during two periods preceding spontaneous, appropriate ICD shocks and during control periods one week later. A total of 107 documented ICD shocks were reported by 42 patients, the majority of whom had coronary artery disease. In the 15-min period preceding shocks, there was a significant incidence of high levels of anger, with odds ratios of 1.83 ($p<0.04$). Other mood states, notably anxiety, worry, sadness, and happiness, did not trigger ICD discharge. Physical activity was also associated with increased incidence of shocks. Correlative findings were reported by Fries et al⁹¹, who found 7-fold increased risk of ICD shock with high levels of physical activity and 9-fold increased risk of ICD shock with mental stress. These observations are consistent with recent experimental⁹² and clinical⁹³ studies, demonstrating that an angerlike state is capable of significantly increasing cardiac electrical instability. In fact, there is an extensive literature indicating that anger is the affective state most commonly associated with sudden cardiac death⁹⁴.

The dynamic influence of mental and physical activity on cardiac electrical function finds further support in a recent study of ambulatory ECG-based T-wave alternans analysis in post-myocardial infarction patients⁹⁵. Modified moving average (MMA) analysis was used to measure TWA from 24-hour AECGs from patients enrolled in the ATRAMI study obtained at an average of 15 days following the index event. The patients were followed for 21 ± 8 months and were matched for gender, age, site of MI, left ventricular ejection fraction, thrombolysis, and beta-adrenergic blockade therapy. A 4- to 7- fold higher odds ratio of cardiac arrest or arrhythmic death was predicted by TWA levels at the 75th percentile of controls or approximately 50microvolts. Individuals at risk for arrhythmic death showed increased TWA levels at maximum heart rate and at 8:00 a.m., suggesting that daily mental and physical stress can disclose clinically significant levels of electrical instability. Although the increase in TWA may be associated with maximum daily heart rate, elevated heart rate per se does not appear to be the sole factor, as TWA measured at peak heart rate did not correlate with the magnitude of the heart rate change nor did the maximum heart rates differ between patients with and without events. These increases in TWA in cases are likely to reflect the influence of enhanced sympathetic nerve activity, since beta-adrenergic receptor blockade reduces TWA magnitude⁹⁶, an effect shown to be independent of heart rate, when this variable was controlled by pacing⁹⁷.

Finally, an important promising and evolving literature of investigations of autonomic and behavioral triggering of ventricular arrhythmias is focused on sleep states, particularly in individuals with apnea and heart failure^{98,99}.

CONCLUSION

Our understanding of the role of the autonomic nervous system has continued to evolve in a fascinating and productive manner. A number of direct benefits in terms of understanding of the function of the autonomic nervous system in health and disease, and quantification of autonomic tone through heart rate variability and baroreceptor function testing by heart rate turbulence analysis show considerable promise in terms of sudden death risk stratification. From the basic science perspective, there appears to be great promise in understanding the organization and function of the intrinsic nervous system and the dynamic nature of nerve sprouting. The pattern of local neurocircuitry is likely to play a critical role in influencing heterogeneity of repolarization, a fundamental factor in arrhythmogenesis. Great strides have been made in the identification and understanding of the cellular and ionic mechanisms by which the autonomic nervous system modulates the genetic substrate responsible for

arrhythmogenesis in the long QT and Brugada syndromes. These advances should lead to better diagnosis and treatment of these syndromes.

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Fig. 1.

Synthesis of new and present views on levels of integration important in neural control of cardiac electrical activity. More traditional concepts focused on afferent tracts (dashed lines) arising from myocardial nerve terminals and reflex receptors (e.g., baroreceptors) that are integrated centrally within hypothalamic and medullary cardiostimulatory and cardioinhibitory brain centers and on central modulation of sympathetic and parasympathetic outflow (solid lines) with little intermediary processing at the level of the spinal cord and within cervical and thoracic ganglia. More recent views incorporate additional levels of intricate processing within the extraspinal cervical and thoracic ganglia and within the cardiac ganglionic plexus, where recently described interneurons are envisioned to provide new levels of noncentral integration. Release of neurotransmitters from postganglionic sympathetic neurons is believed to enhance

excitation in the sinoatrial node and myocardial cells through norepinephrine binding to β_1 -receptors, which enhances adenylyl cyclase (AC) activity through intermediary stimulatory G-proteins (G_s). Increased parasympathectomy outflow enhances postganglionic release and binding of acetylcholine to muscarinic (M_2) receptors, and through coupled inhibitory G-proteins (G_i), inhibits cyclic AMP production (cAMP). The latter alters electrogenesis and pacemaking activity by affecting the activity of specific membrane Na, K, and Ca channels. New levels of integration are shown superimposed on previous views and are emphasized here to highlight new possibilities for intervention. (Reprinted with permission from Blackwell Futura from Lathrop and Spooner 2001.)²

Fig. 2.

Odds ratios for cardiac arrest or sudden death due to arrhythmia in cases *versus* controls for T-wave alternans (TWA) above the 75th percentile measured at maximum heart rate, at 8:00 a.m., and at maximum ST-segment deviation in leads V₁ and V₅. (Reprinted with permission from Blackwell Futura from Verrier et al 2003.)⁹⁵

Fig. 3.

A: Heart rate turbulence in a low-risk post-myocardial infarction (post-MI) patient. B: Blunted heart-rate turbulence in a high-risk post-MI patient. (Reprinted with permission from Kluwer Academic Publishers from Guzik and Schmidt 2002).³⁰

Fig. 4. Transmembrane action potentials and transmural electrocardiograms (ECG) in control and LQT1 (A), LQT2 (B), and LQT3 (C) models of LQTS (arterially-perfused canine left ventricular wedge preparations). Isoproterenol + chromanol 293B - an IKs blocker, d-sotalolol + low $[K^+]_o$, and ATX-II - an agent that slows inactivation of late I_{Na} are used to mimic the LQT1, LQT2 and LQT3 syndromes, respectively. Panels A - C depict action potentials simultaneously recorded from endocardial (Endo), M and epicardial (Epi) sites together with a transmural ECG. BCL = 2000 msec. Transmural dispersion of repolarization across the ventricular wall, defined as the difference in the repolarization time between M and epicardial cells, is denoted below the ECG traces. Panels D-F: Effect of isoproterenol in the LQT1, LQT2

and LQT3 models. In LQT1, isoproterenol (Iso) produces a persistent prolongation of the APD90 of the M cell and of the QT interval (at both 2 and 10 minute), whereas the APD90 of the epicardial cell is always abbreviated, resulting in a persistent increase in TDR (D). In LQT2, isoproterenol initially prolongs (2 minute) and then abbreviates the QT interval and the APD90 of the M cell to the control level (10 minute), whereas the APD90 of epicardial cell is always abbreviated, resulting in a transient increase in TDR (E). In LQT3, isoproterenol produced a persistent abbreviation of the QT interval and the APD90 of both M and epicardial cells (at both 2 and 10 minute), resulting in a persistent decrease in TDR (F). * $p < .0005$ vs. Control; † $p < .0005$, †† $p < .005$, ††† $p < .05$, vs. 293B, d-Sotalol (d-Sot) or ATX-II. (Modified from references ^{82;84;85} with permission).