Review Article

Transient T wave Changes Concerning Arrhythmia

Hirofumi Tasaki MD PhD, Kiyotaka Matsuo MD PhD, Norihiro Komiya MD PhD, Shinji Seto MD PhD, Katsusuke Yano MD PhD

Cardiovascular Medicine, Course of Medical and Dental Sciences Graduate School of Biomedical Sciences, Nagasaki University

T-wave changes are thought to be associated with the repolarization phase of myocardial action potential. Although it has been known that persistent T-wave change is associated with the heart disease or the prognosis, the sensitivity and the specificity are not necessarily satisfactory for clinical therapeutic strategy. Recent basic studies have shown that, in some kinds of pathological states, transient repolarization changes of myocardial action potential were associated with life-threatening arrhythmia. Also clinical studies are being conducted to elucidate the clinical implication of transient T-wave changes on electrocardiography (ECG) in such an arrhythmia. Transient repolarization or T-wave change is thought to occur because of environmental or neurohumoral factors, circadian variation, stretching of myocardium or other triggers in daily life, resulting in fatal arrhythmia. Such fatal arrhythmias are thought to occur under restricted conditions even in the patients with serious heart disease. It is important to clarify and utilize the transient T-wave change directly associated with the fatal arrhythmia on a clinical basis. In this article, we first assess the mechanisms of transient repolarization or T-wave changes on ECG concerning fatal arrhythmia, and afterwards refer to possible attempts at clinical evaluation and application.
(J Arrhythmia 2007; 23: 115–123)

Key words: Fatal arrhythmia, Transient T wave change, Repolarization heterogeneity, Clinical evaluation

Introduction

The etiology of T wave change on electrocardiography (ECG) is thought to relate to various diseases.[1,2] That is, the diseases or pathophysiologies to produce persistent T wave change on ECG include myocardial infarction, hypertrophic or dilated cardiomyopathy, cardiac hypertrophy, WPW syndrome, bundle branch block and long QT syndrome, while those with transient T wave change include angina pectoris, electrolyte imbalance, cardiomyositis, pulmonary embolism, change in autonomic nervous system, pacing arrhythmia and so on.

Although many studies relating to transient T wave change following arrhythmia have been reported, the mechanism is still unknown.[3] For several decades, it has been reported that transient T wave occurs following various arrhythmias or pacing. Leachman et al. assessed the value of postextrasystolic T wave alterations and reported that the frequency of this parameter was not different

Received 26, November, 2006: accepted in final form 1, May, 2007.
Address for Correspondance: Hirofumi Tasaki MD PhD, Cardiovascular Medicine, Course of Medical and Dental Sciences Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: 095-849-7288 Fax: 095-849-7290 Email: tasaki@orange.ocn.ne.jp

between persons with and without coronary heart disease, left ventricular dysfunction or increase in end-diastolic left ventricular pressure, but that they increased as the compensatory pause following the extrasystole lengthened.[3] The transient T wave change recognized after pacing is also reported and it is called cardiac memory (CM),[4] which several researchers have recently studied in detail. According to the studies, the remodeling of the ion channels is thought to play an important part.[5,6] On the other hand, as digital ECG became popular, detection of subtle T wave changes in the patients at high risk for fatal arrhythmia has attracted increasing attention as a prognostic value.[7–10]

In this article, we assess the kinetics of short-time or transient T wave change on ECG leading to arrhythmia, on the basis of findings which have been reported so far, and then refer to possible or ongoing clinical tests trying to detect such pathological transient T wave changes concerning arrhythmias.

Kinetics of transient T wave change

The T wave on ECG corresponds to the repolarization phase of action potential duration (APD). Therefore, the T wave changes according to the factors affecting APD. First of all, we assess the factors which are thought to affect APD and, thus, also the T wave.

1) Cardiac memory

Rosenbaum MB et al. observed that right ventricle pacing produced changes in the spatial heterogeneity of repolarization, manifested as a progressive inversion of the T wave.[4] In their study, maximal T wave appeared after 48 hours of ventricular pacing and it took about 40 days to return to normal form after cessation of pacing. This phenomenon, i.e. T wave change remaining after pacing, was as if the heart had remembered the altered activation sequence during pacing, so it was referred to as 'cardiac memory(CM)'.

This phenomenon is a well established property common to biological organs, which allow them to adapt to their environment and respond to novel stimuli. Such a response was reported in atrial muscle cells.[11–13] It is thought that during atrial fibrillation, persistent changes in electrophysiologcal properties of potassium channels and calcium channels in atrial myocytes occur and result in a shortened atrial refractory period, which is referred to as 'electrical remodeling' relating to maintenance or occurrence of atrial fibrillation.[13]

It has been reported that peculiar changes of APD and ion channels in ventricular myocytes occur as well.[14–16] Shvilkin et al. paced the cardiac ventricles of dogs at rates of 110 to 120 bpm for 3 weeks and reported that (1) recovery time for CM of T wave to return to control form increased in proportion to duration of the previous pacing, (2) the protein synthesis inhibitor cycloheximide markedly attenuated evolution of CM, (3) pacing from the atrium did not produce CM and that (4) CM was associated with increased APD in epicardial and endocardial but not midmyocardial cells. Therefore, they concluded that CM was associated with significant changes of epicardial and endocardial APD resulting in transmural repolarization, and required changes of activation pathways and new protein synthesis.[14] Furthermore, Yu H et al. induced long-term CM in conscious dogs and showed that a decrease in transient outward current (Ito) channel could be associated with the action potential and the T-wave changes of long-term CM.[5] On the other hand, other studies have demonstrated that a short period of ventricular pacing induced heterogeneous changes in APD,[15,16] and that short-term CM was prevented by 4-aminopyridine, which is known to block Ito.[5,17] Recently, angiotensin-converting enzyme inhibition and L type Ca^{2+} channel blockers were also found to prevent memory development in a canine model, while β adrenergic and muscarinic blockers had no effect.[6] Libbus I et al. attributed CM (T wave change) to altered activation sequence resulting in changes of ion channels.[11] Moreover, they insisted on the clinical importance of these changes of ion channels, citing such instances as atrioventricular node ablation for rapid atrial fibrillation, which was associated with bradycardia-dependent ventricular arrhythmia,[18] and biventricular pacing to reduce cardiovascular mortality.[19]

2) Ion channel

In genetic diseases such as long QT syndrome and Brugada syndrome, the gene mutations of ion channels peculiar to the diseases have been partly identified and the dysfunction of ion channel is thought to make the hearts susceptible to fatal arrhythmia.

Also, in heart failure or cardiomegaly, there are several factors, including some kinds of ion channels and various triggers, which contribute to prolonged APD and its abnormal rate-dependent adaptation.[20,21] Further, it is known that the main etiology of APD prolongation is the decrease in the outward current of the K^+ channel and that the APD varies at various cites of the heart, depending on the heterogenous or deviated distribution of some kinds of ion

channels. Qin D et al. made hypertrophied remodeled myocardium after myocardial infarction (MI) in rats and showed that in this model there were prolonged APD, occurring early after depolarization (EAD) depending on stimulation rate, development of delay after depolarization (DAD) depending on stimulation duration under isoproterenol and significant decrease in the density of Ito channel.[22] They suggested reduced Ito could result in prolonged APD. In addition, other researchers reported that the dysfunction of inward rectifier K (Ik_1) channel and delayed rectifier K (Ik_r or Ik_s) channel as well as the decrease in sensitivity of voltage-gated L type Ca channel to β-stimulation, occurred in hypertrophic cardiomyocytes.[23–25]

Furthermore, various triggers are expected to affect action potential. Kamkin A et al. revealed that local stretch lengthened the action potential, depolarized the resting membrane, caused extra systoles, and hence could induce arrhythmia.[26,27] Because the dynamic changes of left ventricular pressure occur during and after tachycardia or premature beats, action potential change along with T wave change and stretch-induced arrhythmia are likely to occur especially in the failing hypertrophic heart. In addition, there are other experimental studies reporting triggered activity following DAD after abrupt cessation of pacing,[21] and EAD with prolonged APD in the hypertrophic heart with chronic AV block under class III antiarrhythmic agents,[28] and clinical studies suggesting a relation with electrophysiological kinetics.[18]

According to these various ion channel remodelings, it seems that APD lengthens, heart rate adaptation worsens, heterogeneity of cardiomyocytes becomes more marked, and that EAD and DAD, as well as automaticity of cardiomyocytes, appear. All of these are likely to result in transient T wave change and increased proarrhythmia.

3) Gap junction

Recent studies have indicated that gap junction, which exists in the intercalated disk and is composed of transmembrane proteins, including connexin 43, determines the electrical and metabolic connection between myocytes and influences the pattern of activation and recovery, depending on its density and distribution.[29] It is known that hypertrophic and ischemic stress on myocytes results in diverse changes of structural proteins in myocardial cells, such as ion channel and gap junction. Recent studies have revealed marked alteration of connexin 43 expression and distribution in ischemic heart disease and hypertrophic cardiomyopathy.[29,30] Uzzaman M et al. investigated the remodeling of the gap junction in hypertrophic hearts and revealed that in contrast to control there was disorganization of connexin 43 and reduction of conduction velocity parallel to the fiber orientation of cardiomyocytes, whereas there was no change of conduction velocity across the fibers, which suggested electrophysiological instability, that is, anisotropic conduction properties.[31,32] In addition, several studies have shown a rapid turn-over of cardiac gap junction proteins, with a half-life of 1–2 hours,[33,34] whereas other studies indicated the anisotropic tissue property determined the location of reentrant ventricular tachycardia in the border zone of MI.[35,36]

Accordingly, those changes of gap junction in post-MI myocytes or hypertrophic myocytes may contribute to development of microreentry and, probably, an increase in the heterogeneity of the refractory period, by inducing differences in the action potentials between different parts of myocardium, which could also produce the substrate for arrhythmia or transient T wave change. In fact, Eloff BC et al. conducted a study using an acidosis model of pig hearts to investigate the effect of ZP123, which enhances gap junction conductance. They demonstrated that ZP123 prevented intercellular uncoupling and repolarization dispersion at the same time, although it had no apparent direct effect on repolarization currents. The results suggest the probability that the enhancement of deteriorated gap junction conductance directly linked to prevention of repolarization dispersion.[37] Several recent studies have shown a rapid turn-over of cardiac gap junction proteins.[33,34] Accordingly, the rapid turnover of the gap junction may be associated with reporalization change and, thus, transient T wave change in the diseased heart.

4) Autonomic nervous function

Many studies of heart rate variability have been conducted to evaluate the effect of the autonomic nervous activities on heart rate,[38] while the studies of muscle sympathetic nerve activity (MSNA) and heart rate turbulence (HRT) have been conducted to evaluate fluctuation of autonomic function after arrhythmia, in particular the ventricular premature beat.

It is known that the fluctuation of autonomic nervous function occurs after ventricular premature beats due to the simultaneous change of blood pressure.[39] Welch WJ et al. induced ventricular premature beats in patients undergoing electrophysiologcal studies (EPS) and, at the same time, recorded muscle sympathetic nerve activity (MSNA)

from the peroneal nerve. The results showed a single ventricular premature beat was followed by a burst of sympathetic activity and afterwards, nearly complete neural silence appeared during several postextrasystolic sinus beats.[40] These abrupt bursts are thought to be the positive feedback of sympathetic nerves, which is conducted via efferent sympathetic nerves about 2 seconds after sensing transient decrease of blood pressure at baroreceptors. Considering the conduction velocity of sympathetic nerves and the length of the feedback loop, the positive feedback is expected to reach the heart around one second after the ventricular premature beat. In addition, Smith ML et al. induced ventricular tachycardias in 16 patients and recorded MSNA during ventricular tachycardia. In the study, large surges appeared in direct proportion to arterial pressure reductions and contributed to hemodynamic stability during ventricular tachycardia.[41] Accompanying ventricular arrhythmias, an abrupt burst of activity is thought to occur in peripheral sympathetic nerves of the organs as well as the heart. Therefore, once ventricular arrhythmias occur, during the following one to two seconds the surge of sympathetic activity affects repolarization of cardiac myocytes and thus could change T wave morphology in pathological cardiac states such as myocardial infarction, cardiac hypertrophy and heart failure.[39,42]

Schwartz PJ et al. pointed out the efficacy of the left cardiac sympathetic denervation from the point of view of 'sympathetic imbalance hypothesis' as well as 'intracardiac abnormality hypothesis', and insisted on the importance of sympathetic nervous systems in triggering lethal arrhythmia, probably via an α-adrenergic-mediated mechanism.[43] Miyazaki T et al. tested the effect of autonomic nerve on ST elevation under various conditions using several drugs and suggested the presence of an area of early repolarizasion causing ST elevation in Brugada syndrome.[44]

The findings mentioned above indicate that the dynamic fluctuation of autonomic nervous function occurs and could affect the repolarization phase and transient T wave change in the healthy heart, as well as under pathological conditions.

Attempt at clinical evaluation of transient T wave change

As mentioned above, there seem to be various latent changes in the repolarizasion phase of action potential and T wave morphology on ECG, relating to fatal or non-fatal arrhythmia in patients with various heart diseases. All of these kinds of kinetics may produce short-time change of repolarization or transient T wave change. How could we detect and evaluate such a subtle and transient change of the T wave on ECG or the repolarizasion phase of action potential in the clinical setting? Below are examples of ongoing attempt at clinical evaluation of T waves on ECG.

1) Monophasic action potential

Monophasic action potential (MAP) is recorded by an electrode in direct contact with the myocardium and it is thought to reflect the average action potential of the myocardium within several millimeters around the contact electrode.[45] Many experimental studies by means of this method have shown the epicardial or transmural dispersions of APD. The relationship between the abnormality of action potential or MAP and that of the ST-T-U complex on ECG has been hypothesized as follows.

Antzelevitch C et al. divided the myocardium into three layers (epicardial, M-region, endocardial sites) and explained that the abnormality of ST-T-U in hereditary cardiac diseases could be derived from the gradient of the action potential between the three layers.[46,47] That is to say, Yan GX et al. recorded the action potential of those three sites separately in canine left ventricular wedge models of long QT syndrome. They found that the end of repolarization of the epicardium was coincident with the peak of the T wave, while the end of repolarization of M cells was coincident with the end of the T wave.[46] They also demonstrated that various ion channel modulators produced epicardial and transmural dispersion of action potential which resulted in ventricular tachycardia or ventricular fibrillation as in Brugada syndrome. The study showed that depression of the action potential dome in the right ventricular epicardium created a transmural voltage gradient between epicardium and endocardium, which is thought to be responsible for the ST segment elevation in Brugada syndrome.[47]

On the other hand, Kurita T and Shimizu W et al. recorded the epicardial monophasic action potentials of the right venricular out flow tract in three Brugada patients using contact electrodes during open-chest surgery. They documented the typical configuration of Brugada syndrome from the epicardial sites in all Brugada patients, but not in control patients.[48] Yan GX et al. explained that ventricular repolarization ST-T-U components on the ECG dynamically change in morphology under various pathophysiological conditions and play an important role in the development of ventricular arrhythmia.[49] They introduced the clinical manifestations of early

repolarization syndrome and Brugada syndrome upon the patients, and tried to identify the ionic and cellular basis for the ventricular repolarization component on the body surface ECG in humans under normal and phathological conditions. They inferred the dynamic mechanisms of development of fatal ventricular arrhythmia with the use of a monophasic action potential as described in several papers.

These studies clarified from an electrophysiological point of view how the spatial dispersion of the action potential and its duration in long QT syndrome and Brugada syndrome could appear as ST-T change. If the relation between the electrophysiological findings on action potential and standard ECG is elucidated more precisely and in detail, we might develop a more profound understanding of not only persistent but also transient T wave change.

2) Contemporary computational T wave analyses

As most of standard 12-lead ECGs have been recorded as digital data in the past decade, several attempts to document fine electrophysiological heterogeneity in the pathological myocardium have been made in analyses of T wave changes.[7–10,50–52)]

Kors JA et al. investigated some risk factors including T wave axis and QT interval in 5781 participants (2352 men; 3429 women) from the population-based Rotterdam Study followed up for 3–6 (mean 4) years, and pointed out the prognostic importance of the T wave axis for fatal and non-fatal cardiac events.[7)] Zabel M et al. recorded the standard digital ECG of 280 consecutive post-MI patients and analyzed T wave loop dispersion [the number of the subdivisions on which a T wave loop passes in the rectangle divided into 100 subdivision], total cosine R-to-T (TCRT) [the vector deviation between the depolarization wave and dominant repolarization wave determined by calculating cosine value between the 3-dimensional R- and dominant T-wave loop vectors during depolarization period within the optimized decomposition space], three other T wave morphology descriptors and their prognostic value. The study indicated that T wave loop dispersion and TCRT had prognostic value.[8)] Moreover, another T wave descriptor, i.e. T wave residuum (TWR), was proposed from the field of biomedical engineering.[50,51)] This descriptor is one of two components: the 3-dimensional dipolar component and the non-dipolar component, decomposed and then reconstructed on the basis of vectorial and algebraic concepts from the digital 12-lead ECG (from 8 leads: I, II, V1, V2. . ..V6). The TWR, which is the residual component left after the dipolar component is reconstructed in the 3-dimensional space from the digital data of ECG, is expected to contain the information of electrophysiological heterogeneity of pathological cardiac muscle. Malik M et al., assuming QT dispersion as the descriptor of the dipolar component and TWR as the descriptor of the non-dipolar component, conducted the study on subjects with hypertrophic cardiomyopathy, dilated cardiomyopathy and acute MI, comparing them with normal subjects. They showed clear and significant differences in TWR between those four groups of subjects and no correlation between TWR and QT dispersion in the subjects, except in hypertrophic cardiomyopathy ($p = 0.03$).[51)] Recently, Zabel M et al. assessed the prognostic value of TWR as well as other parameters, such as T wave loop dispersion, T wave morphology dispersion, T wave loop area, QT interval and TCRT in 813 male US veterans with cardiovascular disease by means of digital 12-lead ECG. The study revealed TWR had long-term independent prognostic value among these clinical variables in the patients with cardiovascular diseases.[9)]

Moreover, Smetana P et al. conducted 12-lead Holter monitoring in 60 healthy subjects to investigate repolarization heterogeneity and its circadian patterns.[52)] They calculated TWR, which was thought to be regional repolarization heterogeneities and to partly constitute T wave, and observed that TWR was greatest in the morning hours. The results revealed that the transient repolarization changes calculated from digital ECG data, constituting transient T wave changes, greatly fluctuated and went up to the maximum value in the morning, which implied a higher susceptibility to arrhythmic events in the morning hours. Therefore, these data may also suggest the transient change of digital information derived from T waves on 12-lead ECG is associated with transient ventricular repolarization heterogeneity change.

3) T wave alternans

For a long time, it has been reported that clear manifestation of T wave alternans (TWA) appears on ECG just before ventricular fibrillation (VF). In 1984, Adam DR et al. invented a novel computerized system which detected beat–to-beat TWA. They computed T wave fluctuation by means of power spectrum analysis in dogs and concluded that the statistical analysis of T wave morphology might provide a sensitive probe of ventricular vulnerability to fibrillation.[53)] Rosenbaum DS et al. conducted exercise stress tests to record TWA, as well as EPS, in 83 patients, including 53 patients with coronary

heart disease. They showed that the manifestation of TWA in exercise test was consistent with the results of EPS and might serve as a noninvasive marker of vulnerability to ventricular arrhythmias.[54] On the other hand, Kaufman ES et al. reported that TWA appeared at a patient-specific heart rate threshold related to pacing rate rather than sympathetic activation, and rose in amplitude at a higher heart rate.[55] Tanno K et al. and Bloomfield DM et al. evaluated the sensitivity and the specificity of the TWA test for better risk stratification.[56,57] They concluded that microvolt TWA could identify not only a high-risk group but also a low-risk group by setting the proper thresholds. In 1999, Pastore JM et al. monitored the cellular membrane potential of pacing-induced TWA in an intact heart model of guinea pig and observed that TWA arose from reporalization alternans at the level of single cell rather than depolarization alternans, and further that membrane repolarization was alternating with the opposite phase between neighboring regions of cardiomyocytes, i.e. discordant alternation.[58,59] Afterwards, Nearing BD et al. conducted a study in dogs with left coronary artery occlusion and right atrial pacing at 150 bpm and showed that when TWA in an ABAB pattern reached a certain high magnitude, a stepwise change in complexity to tripling (ABCABC), quadrupling (ABCDABCD) or more complex forms occurred, with episodes of discordant TWA culminating in VF.[60] Recently, Nemec JN et al. conducted an intriguing study concerning T wave oscillations.[10] They sought to measure the non-periodic T wave oscillation during exercise stress test in 23 long QT syndrome patients [genotype:LQT1(13),LQT2(7) and LQT3(3)] and 16 healthy subjects under administration of phenylephrine and dobutamine, and reported that significantly high non-periodic T wave oscillations were observed in the patients at clinically high risk for fatal arrhythmia. They inferred that T wave oscillations in the study might have originated from differences in action-potential and diastolic-interval (AP-DI) property and in electrical interaction between the different segments of ventricle or EAD in a relatively small population of myocardial cells. If we could detect and elucidate these complex forms of TWA emerging just before the development of fatal arrhythmia in humans, we might obtain the critical preventive measure of lethal arrhythmia or sudden cardiac death in clinical medicine.

4) QT dynamics

Many studies relating to the QT interval have been conducted. The QT interval changes according to various factors, such as the autonomic nervous system, gender, age, drug and metabolism.[61] There are so many factors affecting the repolarization phase of myocardium that controversy persists regarding QT interval as a risk factor for life-threatening arrhythmia or sudden cardiac arrest.[61–64]

In addition, the QT interval changes beat by beat depending on the heart rate, and the heart rate oscillates dynamically during daily activities. Accordingly, the precise method for evaluating the effect of heart rate on QT interval is to measure the QT interval with heart rate fixed by pacing, although it has been reported that it takes about 2 minutes for the QT interval to completely adapt to the new pacing rate.[45,65] Recently, Batchvarov VN et al. assessed the relationships between QT interval and RR interval (QT/RR) and reported that the formulae calculated for individuals might be necessary because QT/RR varies individually.[63,64]

Mechanisms and clinical application of T wave kinetics

As we mentioned above, T wave changes concerning arrhythmia are related to the phenomena of repolarization phase of myocardium. In past decades, many kinds of kinetics relative to the repolarization phase have been revealed in detail.

Recent studies on action potential, ion channel and gap junction in myocardium or myocardial cells have gradually revealed the abnormal process of the repolarization phase in various pathophysiological states. In the myocardium of hypertrophic or ischemic heart disease, ion channel remodeling occurs and the prolongation of APD or an abnormal heart rate adaptation appears. In addition, conduction velocity in the parallel direction to the myocardial fiber orientation may decrease due to reduction of the gap junction mainly composed of connexin 43, which could affect the dispersion of the repolarization phase at the same time. All these changes might make the repolarization time of myocardium heterogeneous. In myocardium with such an arrhythmogenic substrate, several triggers, such as a premature beat, stretching of myocardium, tachycardia, bradycardia and AV block, may enhance the prolongation of APD or abnormal heart rate adaptation, and cause transient abnormal potential change, including EAD and DAD, both of which result in more spatial and transient heterogeneity in the myocardium and, thus, transient T wave changes. Additionally, it has been reported that TWA arises from reporalization alternans at the level of single cells even in the intact heart. In vivo, other complicated and neurohumoral

factors, such as autonomic tone variations, may play an important role in the occurrence of life-threatening arrhythmia accompanied by transient T wave changes. Recent studies have been clarifying the mechanisms of such transient repolarization changes in the heart just before fatal arrhythmia develops.

On the other hand, various attempts emerged to elicit significant digital data included in subtle T wave changes and to utilize them for predictive index of cardiac events or fatal arrhythmias, as digital ECG has become popular lately.[66] Part of the foci of the attempts to detect T wave abnormality seems to be moving on from macro T wave change to micro or subtle and transient T wave change. The subtle but significant and independent information included in T wave data on the ECG seems to be a critical clue to lead to reasonable clinical understanding or resolution of fatal arrhythmia.

These kinetics and mechanisms to link the transient T wave change with the development to fatal arrhythmia are being recognized in the electrophysiological field. However, as it stands now, there is not enough evidences to definitely affirm that these transient and real-time T wave changes mentioned above are linked to life-threatening arrhythmia. At present or in the near future, how precisely can EPS and ECG detect fatal-arrhythmia-related myocardial repolarization changes, which might be derived from diverse electrophysiological etiologies, and might change at every moment under various circumstances? The elucidation of those electrophysiological phenomena and the clinical application remain crucial issues.

Acknowledgement

We greatly thank Professor Marek Malik and Professor A John Camm, Division of Cardiac and Vascular Sciences, St. George's University of London, UK, for their kind comments and suggestions.

References

1) Katz AM: T wave "memory": Possible causal relationship to stress-induced changes in cardiac ion channels? J Cardiovasc Electrophysiol 1992; 3: 150–159
2) Goldberger AL: Myocardial infarction electrocardiographic differential diagnosis. 4th eds. The Mosby-Year Book, Inc, 1991
3) Leachman DR, Dehmer GJ, Firth BG, et al: Evaluation postextrasystolic T wave alterations in identification of patients with coronary aretery disease of left ventricular dysfunction. Am Heart J 1981; 102(4): 658–663
4) Rosenbaum MB, Blanco HH, Elizari MV, et al: Electronic modulation of the T wave and cardiac memory. Am Heart J 1982; 50: 213–222
5) Yu H, McKinnon D, Dixon JE, et al: Transient outward current, I_{to1}, is altered in cardiac memory. Circulation 1999; 99: 1898–1905
6) Rosen MR, Cohen IS: Cardiac memory ... new insights into molecular mechanisms. J Physiol 2006; 570(Pt 2): 209–18
7) Kors JA, de Bruyne MC, Hoes AW, et al: T axis as an indicator of risk of cardiac events in elderly people. Lancet 1998; 352: 601–605
8) Zabel M, Acar B, Klingenheben T, et al: Analysis of 12-leade T-wave morphology for risk stratification after myocardial infarction. Circulation 2000; 102: 1252–1257
9) Zabel M, Malik M, Hnatkova K, et al: Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. Circulation 2002; 105: 1066–1070
10) Nemec J, Hejlik JB, Shen WK, et al: Catecholamine-induced T-wave lability in congenital long QT syndrome: A novel phenomenon associated with syncope and cardiac arrest. Mayo Clin Proc 2003; 78: 40–50
11) Libbus I, Rosenbaum MB: Remodeling of cardiac repolarization: Mechanisms and implications of memory. Card Electrophysiol Rev 2002; 3(6): 302–310
12) Fareh S, Villemaire C, Nattel S: Improtance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. Circulation 1998; 98: 2202–2209
13) Herweg B, Chang F, Chandra P, et al: Cardiac memory in canine atrium-Identification and implications. Circulation 2001, 103: 455–461
14) Shvilkin A, Danilo P, Wang J, et al: Evolution and resolution of long-term cardiac memory. Circulation 1998; 97: 1810–1817
15) Costard-Jaeckle A, Goetsch B, Antz M, et al: Slow and long-lasting modulation of myocardial repolarization produced by ectopic activation in isolated rabbit hearts-evidence for cardiac "memory". Circulation 1989; 80: 1412–1420
16) Goyal R, Syed ZA, Mukhopadhyay PS, et al: Changes in cardiac repolarization following short periods of ventricular pacing. J Cardiovasc Electrophysiol 1998; 9: 269–280
17) Del Balzo U, Rosen MR: T wave changes persisting after ventricular pacing in canine heart are altered by 4-aminopyridine but not by lidocaine. Implications with respect to phenomenon of cardiac 'memory'. Circulation 1992; 85: 1464–1472
18) Ozcan C, Jahangir A, Friedman PA, et al: Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med 2001; 344: 1043–1051
19) Leclercq C, Cazeau S, Le Breton H, et al: Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 1998; 32: 1825–1831
20) Hiraoka M: Modulation of electrical properties by ions, hormons and drugs. In PageE, Fozzard HA & Solaro RJ ed.: Handbook of Physiology. Section 2. The Cardiovascular System, Volume I. The Heart. American Physiological Society, Oxford, 2002, p 595–653
21) Vermeulen JT: Mechanism of arrhythmias in heart

failure. J Cardiovasc Electrophysiol 1998; 9: 208–221
22) Qin D, Zhang ZH, Caref EB, et al: Cellular and ionic basis of arrhythmias in postinfarction remodeled ventricular myocardium. Circ res 1996; 79: 461–473
23) Kaab S, 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; 78: 262–273
24) Tsuji Y, Opthof T, Kamiya K, et al: Pacing-induced heart failure causes a reduction of delayed rectifier potassium currents along with decreases in calcium and transient outward currents in rabbit ventricle. Cardiovasc Res 2000; 48: 300–309
25) Piot C, Lemaire S, Albat B, et al: High frequency-induced upregulation of human cardiac calcium currents. Circulation 1996; 93: 120–128
26) Kamkin A, Kiseleva I, Isenberg G: Stretch-activated currents in ventricular myocytes: amplitude and arrhythmogenic effects increase with hypertrophy. Cardiovasc Res 2000; 48: 409–420
27) Zabel M, Koller BS, Sachs F, et al: Stretch-induced voltage changes in the isolated beating heart: importance of the timing of stretch and implications for stretch-activated ion channels. Cardiovasc Res 1996; 32: 120–130
28) Volders PG, Sipido KR, Vos MA, et al: Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. Circulation 1998; 98: 1136–1147
29) Severs NJ: Pathophysiology of gap junctions in heart disease. J Cardiovasc Electrophysiol 1994; 5: 462–475
30) Peters NS: New insights into myocardial arrhythmogenesis: distribution of gap-junctional coupling in normal, ischaemic and hypertrophied human hearts. Clin Sci 1996; 90: 447–452
31) Uzzaman M, Honjo H, Takagishi Y, et al: Remodeling of gap junctional coupling in hypertrophied right ventricles of rats with monocrotaline-induced pulmonary hypertension. Circ Res 2000; 86: 871–878
32) Emdad L, Uzzaman M, Takagishi Y, et al: Gap junction remodeling in hypertrophied left ventricles of aortic-banded rats: prevention by angiotensin II type 1 receptor blockade. J Mol Cell Cardiol 2001; 33: 219–231
33) Darrow BJ, Laing JG, Lampe PD, et al: Expression of multiple connexins in cultured neonatal rat ventricular myocytes. Circ Res 1995; 76: 381–387
34) Beardslee MA, Laing JG, Beyer EC, et al: Rapid turnover of connexin43 in the adult rat heart. Circ Res 1998; 83: 629–635
35) Dillon SM, Allessie MA, Ursell PC, et al: Influences of anisotropic tissue structure on reentrant circuits in the epicardial border zone of subacute canine infarcts. Circ Res 1988; 63: 182–206
36) Peters NS, Coromilas J, Severs NJ, et al: Disturbed connexin43 gap junction distribution correlates with the location of reentrant circuits in the epicardial border zone of healing canine infarcts that cause ventricular tachycardia. Circulation 1997; 95: 988–996
37) Eloff BC, Gilat E, Rosenbaum DS, et al: Pharmacological modulation of cardiac gap junctions to enhance cardiac conduction: evidence supporting a novel target for antiarrhythmic therapy. Circulation 2003; 108: 3157–3163
38) Task force of the European Society of Cardiology the North American Society of pacing Electrophysiology: Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043–1065
39) Grassi G, Seravalle G, Bertinieri G, et al: Sympathetic response to ventricular extrasystolic beats in hypertension and heart failure. Hypertension 2002; 39: 886–891
40) Welch WJ, Welch WJ, Smith ML, et al: Enhancement of sympathetic nerve activity by single premature ventricular beats in humans. J Am Coll Cardiol 1989; 13: 69–75
41) Smith ML, Ellenbogen KA, Beightol LA, et al: Sympathetic neural responses to induced ventricular tachycardia. J Am Coll Cardiol 1991; 18: 1015–1024
42) Greenwood JP, Scott EM, Stoker JB, et al: Hypertensive left ventricular hypertrophy: relation to peripheral sympathetic drive. J Am Coll Cardiol 2001; 38: 1711–1717
43) Schwartz PJ, Locati EH, Moss AJ, et al: Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. Circulation 1991; 84: 503–511
44) Miyazaki T, Mitamura H, Miyoshi S, et al: Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996; 27: 1061–1070
45) Ino T, Karagueuzian HS, Hong K, Meesmann M, et al: Relation of monophasic action potential recorded with contact electrode to underlying transmembrane action potential properties in isolated cardiac tissues: a systematic microelectrode validation study. Cardiovasc Res 1988; 22: 255–64
46) Yan GX, Antzelevitch C: Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998; 98: 1928–1936
47) Yan GX, Antzelevitch C: Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999; 100: 1660–1666
48) Kurita T, Shimizu W, Inagaki M, et al: The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. J Am Coll Cardiol 2002; 40: 330–334
49) Yan GX, Lankipalli RS, Burke JF, et al: Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. J Am Coll Cardiol 2003 6; 42: 401–409
50) Acar B, Koymen H: SVD-based on-line exercise ECG signal orthogonalization. IEEE Trans Biomed Eng 1999; 46: 311–321
51) Malik M, Acar B, Gang Y, et al: QT dispersion does not represent electrocardiographic interlead heterogeneity of ventricular repolarization. J Cardiovasc Electrophysiol 2000; 11: 835–843
52) Smetana P, Batchvarov VN, Hnatkova K, et al: Sex differences in repolarization homogeneity and its circadian pattern. Am J Physiol 2002; 282: H1889–1897
53) Adam DR, Smith JM, Akselrod S, et al: Fluctuations in

T-wave morphology and susceptibility to ventricular fibrillation. J Electrocardiol 1984; 17: 209–218
54) Rosenbaum DS, Rosenbaum DS, Jackson LE, et al: Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994; 330: 235–241
55) Kaufman ES, Mackall JA, Julka B, et al: Influence of heart rate and sympathetic stimulation on arrhythmogenic T wave alternans. Am J Physiol 2000; 279: H1248–1255
56) Tanno K, Ryu S, Watanabe N, et al: Microvolt T-wave alternans as a predictor of ventricular tachyarrhythmias: a prospective study using atrial pacing. Circulation 2004; 109: 1854–1858
57) Bloomfield DM, Bigger JT, Steinman RC, et al: Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006; 47: 456–463
58) Pastore JM, Girouard SD, Laurita KR, et al: Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999; 99: 1385–1394
59) Hirayama Y, Saitoh H, Atarashi H, et al: Electrical and mechanical alternans in canine myocardium in vivo. Dependence on intracellular calcium cycling. Circulation 1993; 88: 2894–2902
60) Nearing BD, Verrier RL: Progressive increases in complexity of T-wave oscillations herald ischemia-induced ventricular fibrillation. Circ res 2002; 91: 727–732
61) Blanche PM, Coumel P: T wave dinamicity: Risk of arrhythmia and sudden death: Malik M, ed. London, BMJ, 2001 pp 249–255
62) Smetana P, Batchvarov V, Hnatkova K, et al: Circadian rhythm of the corrected QT interval: impact of different heart rate correction models. Pacing Clin Electrophysiol. 2003; 26: 383–386
63) Batchvarov VN, Ghuran A, Smetana P, et al: QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol 2002; 282: H2356–H2363
64) Batchvarov V, Malik M: Individual Patterns of QT/RR Relationship. Card Electrophysiol Rev 2002; 6: 282–288
65) Franz MR, Burkhoff D, Spurgeon H, et al: In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. Eur Heart J 1986; 7: 34–41
66) Malik M: Assessment of T-wave morphology, Mayo Clin Proc 2003; 91: 18–20