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Cardiac electrical remodeling in health and disease

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Abstract

Electrical remodeling of the heart occurs in response to both functional (i.e. altered electrical activation) and structural (i.e. heart failure, myocardial infarction, etc.) stressors. These electrophysiological changes produce a substrate that is vulnerable to malignant ventricular arrhythmias. Understanding the cellular and molecular mechanisms of electrical remodeling is important in elucidating potential therapeutic targets designed to alter maladaptive electrical remodeling. For example, primarily electrical remodeling occurs in response to altered patterns of electrical activation without significant structural remodeling. In contrast, secondary remodeling arises in response to a structural insult. In this article, we review cardiac electrical remodeling (primarily in the ventricle) with an emphasis on the mechanisms responsible for these adaptations. These mechanisms suggest novel therapeutic targets to manage or prevent the most devastating manifestation of heart diseases, sudden cardiac death (SCD).

Introduction

In recent years, cardiovascular death rates have fallen, and yet the proportion of cardiovascular death that is attributable to sudden cardiac death (SCD) is on the rise [1]. It is estimated that the incidence of sudden cardiac death is approximately 350,000 events per year in the United States. The most common etiology of SCD is the development of malignant ventricular arrhythmias resulting from complex structural and electrical remodeling that follows myocardial injury, most commonly secondary to coronary artery disease. Cardiac remodeling is often an adaptive response to a functional or structural stressor and plays an important role in both cardiovascular health and disease. Initially, these adaptations compensate and maintain cardiac performance, but over time, they can become maladaptive, causing progressive pump failure and/or malignant arrhythmias. Structural remodeling of the heart has been extensively reviewed and is beyond the scope of this paper [2,3]. In addition to remodeling of mechanical and contractile properties of the heart, it has been more recently appreciated that various disease states can remodel key electrophysiological properties of the heart. Electrical remodeling occurs in both the atria and ventricle. Electrical remodeling in the atria has been linked to atrial arrhythmias such as atrial fibrillation and has been recently reviewed [4,5]. In the ventricle, electrical remodeling produces an electrophysiological substrate for the development of potentially lethal ventricular arrhythmias. Therefore, in this article, we review cardiac electrical remodeling

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primarily in the ventricle, with an emphasis on the mechanisms responsible for these adaptations. We also discuss possible novel therapeutic targets to manage the consequence of ventricular electrical remodeling such as ventricular arrhythmias which lead to SCD.

Basic electrophysiological properties of the heart

Normal electrical conduction in the heart allows for the coordinated propagation of electrical impulses that initiate atrial and ventricle contraction. The surface electrocardiogram (ECG) is a reflection of these cellular electrical events (Figure 1). For example, atrial depolarization is represented by the p-wave on the ECG. Ventricular depolarization and repolarization represented the QRS complex and T-wave, respectively. At the cellular level, the cardiac action potential is characterized by the interplay of depolarizing and repolarizing currents (Figure 1). In ventricular myocytes (i.e. QRS complex and T wave), activation of the Na+ current causes rapid depolarization (phase 0) followed by a brief period of repolarization (phase 1) secondary to activation of transient outward K+ current (I_{to}). Subsequently, depolarization is maintained (phase 2) by a balance of inward L-type Ca^{2+} current ($I_{Ca\text{-}L}$) and outward K^+ currents (primarily I_{kr} but also I_{Ks}). Finally, repolarization (phases 3 and 4) occurs in response to inactivation of $I_{Ca\text{-}L}$ and activation of multiple outward K^+ currents (I_{Kr}, I_{Ks} and I_{K1}). The subsequent of sections of this review will consider how these electrical properties of the heart remodel in health and disease.

Electrical remodeling of the heart

Electrical remodeling can be divided into primary and secondary remodeling (Figure 2). *Primary electrical remodeling* describes electrical remodeling that occurs primarily in response to a functional insult, such as an altered sequence of electrical activation. For example, during right ventricular pacing the normal sequence of electrical activation is altered because the initiating electrical impulse arises from ventricular myocytes in the right ventricle and not through the specialized purkinje system. In general, this type of electrical remodeling occurs in the absence of a primary structural insult to the myocardium [6,7]. By contrast, *secondary electrical remodeling* develops as a result of a structural alteration such as heart failure (HF), hypertrophy, or myocardial infarction (54). The mechanisms responsible for primary and secondary electrical remodeling are complex and remain to be fully elucidated. However, recent research has shown that primary electrical remodeling also occurs in the absence of structural remodeling, and has provided important insights into the mechanisms underlying electrical remodeling of the heart in disease [8]. Furthermore, understanding the cellular and molecular mechanisms of electrical remodeling is important in elucidating potential therapeutic targets. Utilizing these insights to develop therapies designed to alter maladaptive electrical remodeling could transform the management of malignant arrhythmias.

Primary electrical remodeling

For the purpose of this review, we define electrical remodeling as a persistent change in the electrophysiological properties of the heart in response to a change in the sequence of electrical activation. As stated above, if these changes occur in the absence of significant structural changes, they are referred to as *primary electrical remodeling.* Also, changes in the rate of electrical activation can lead to primary electrical remodeling. This review will primarily focus on the role of altered sequence of electrical activation, and the reader is referred to recent reviews on the role of altered rate of activation in primary electrical remodeling [9,10]. Nearly 30 years ago, Rosenbaum, *et al.* described remodeling of cardiac repolarization in response to altered activation [9]. Specifically, following prolonged right ventricular (RV) pacing, the polarity of the T wave on the electrocardiogram (ECG) changes was persistently inverted even when normal activation was restored (Figure 3). This

phenomenon was termed “cardiac memory” because the T wave polarity “remembered” the QRS polarity during the previous period of pacing [9]. The occurrence of cardiac memory represents significant remodeling of myocardial repolarization and occurs within minutes to hours of altered electrical activation (i.e. short-term memory)[10]. Furthermore, long periods of altered activation induce greater magnitude of T wave remodeling that persists for weeks to months (i.e. long-term memory)[10]. Understanding the mechanisms underlying cardiac memory, a clinical manifestation of primary electrical remodeling, might provide insights into the mechanisms underlying more complex electrical remodeling (i.e. secondary remodeling) as occurs following structural insults such as myocardial infarction.

During normal activation of the ventricle through the His-Purkinje system, there is rapid electrical activation of both ventricles to produce synchronize mechanical contraction. In disease states that affect the cardiac conduction system or ventricular pacing, the propagation of impulse occurs through cell-to-cell conduction. The myocardial region from which activation initiates serves as the source, and the remainder of the myocardium becomes the sink. This generates a source-sink mismatch in which downstream depolarizing myocytes exert an electrotonic influence that prolongs repolarization in myocytes that are adjacent to the source [11–13]. Consequently, there is action potential prolongation in regions adjacent to the site of altered activation and shortening in distal regions [13]. The altered repolarization gradients that develop likely cause change in T-wave polarity. Electrotonus occurs within minutes after onset of altered activation and serves as a trigger for electrical remodeling (i.e. ion channel changes). The mechanisms responsible for specific ion channel remodeling in response to electrotonus is an active area of investigation. For example, attenuation of the epicardial phase 1 notch is evident within minutes after onset of altered activation [12,14]. This is due to a decrease in the transient outward K^+ current (I_{to}) in myocardial regions adjacent to site of altered activation [15]. The importance of I_{to} remodeling in short-term cardiac memory is supported by the observation that treatment with the I_{to} blocker 4-amino-pyridine prevents short-term memory, and that neonatal dogs which lack I_{to} are resistant to cardiac memory [15,16].

Another important consequence of altered electrical activation is changes in the mechanical contractile properties of the heart, a process known as stretch-dependent remodeling [17]. Specifically, during altered activation, myocardial regions that are adjacent to the site of altered activation exhibit reduced mechanical strain, whereas distal regions are under significantly greater strain [8,17]. Our laboratory recently investigated whether the changes in regional mechanical strain could induce electrical remodeling through a mechano-electrical feedback mechanism. Interestingly, we found that the most significant action potential remodeling occurred in myocardial regions that were under enhanced mechanical strain [8]. These findings were also evident in the pacing-induced model of dyssynchronous HF, in which the late-activated lateral LV region exhibits the most significant action potential remodeling [18]. Furthermore, recent studies have identified that short periods of mechanical stretch can also induce cardiac memory [19]. These observations suggest an important role for mechanical strain/stretch in inducing cardiac electrical remodeling.

Myocardial stretch is a potent stimulus for the local release of angiotensin II, and treatment with angiotensin receptor blockers attenuates the development of “short-term” memory [20,21]. Importantly, angiotensin II was recently shown to decrease I_{to} in isolated epicardial myocytes. Following incubation with angiotensin II, I_{to} density was reduced with altered kinetics and attenuation of the phase1 notch was evident in epicardial myocytes [21]. Furthermore, the angiotensin II receptor (AT1) co-localizes to the α subunit (Kv4.3) of the channel carrying I_{to}, and exposure to angiotensin II caused internalization of the AT1 – Kv4.3 complex [22]. Angiotensin II also has a role in regulation of the β-subunit (KChIP2) through CREB mediated transcriptional regulation [23–25]. Therefore, angiotensin-

converting enzyme (ACE) inhibitors or angiotensin receptor blockers could have a beneficial role in prevention of cardiac memory.

In contrast to short-term memory, the ionic bases for chronic remodeling are complex and involve altered outward K^+ currents, inward Ca^{2+} currents and changes in the quantity and distribution of cardiac gap junctions. The remodeling of the early-activated region following long-term pacing has been extensively studied; however, changes in the late-activated region remain to be fully elucidated. In long-term memory, remodeling of I_{to} results in a decreased current density, altered activation threshold (i.e. more positive) and delayed recovery from inactivation [15]. Furthermore, the rapid component of the delayed rectifier current (I_{Kr}) is remodeled in “long-term” memory [26]. Specifically, the normal transmural gradient of greater I_{Kr} in the epicardium compared to the endocardium is reversed in long-term memory [26]. In addition to the remodeling of outward K^+ currents, long-term memory is associated with remodeling of the inward L-type Ca^{2+} current (I_{ca})[27]. In fact, treatment with L-type Ca^{2+} channel blockers has been shown to attenuate both short- and long-term cardiac memory [27]. Interestingly, only in long-term cardiac memory is the function of the L-type Ca^{2+} channel remodeled, and thus, the role of $I_{Ca,L}$ in short-term memory is not clear. In long-term cardiac memory, $I_{Ca,L}$ activates at a more positive membrane voltage, and recovery from inactivation is prolonged, both of which will prolong action potential duration (APD)[27]. It is postulated that the mechanisms responsible for these changes in $I_{Ca,L}$ are secondary to the reduction of KChIP2, which has recently been shown to be an accessory subunit for the L-type Ca^{2+} channel [28].

Furthermore, Patel *et al.* demonstrated remodeling of the gap junction protein, connexin 43 (Cx43), following prolonged RV pacing [29]. They found reduced Cx43 expression primarily in the early activated myocardial segments. By contrast, Spragg *et al.* showed that Cx43 protein expression is not decreased in the late-activated myocardial segments, but its localization is lateralized with a reduction in conduction velocity in these regions[30]. The mechanisms responsible for Cx43 remodeling remain unclear, but angiotensin II has been postulated as a likely modulator of Cx43 in cardiac memory. Whether experimental agents that augment gap junction conduction will have a role in attenuating cardiac memory remains to be explored.

In summary, primary electrical remodeling occurs in response to alteration in the pattern of electrical activation (Figure 2). These changes alter electrotonic flow and myocardial strain throughout the heart, triggering distinct myocardial remodeling in the early-activated vs. late-activated regions. Electrotonic remodeling is apparent in early-activated regions, while mechanical strain-dependent remodeling occurs in the late-activated regions. These triggers underlie remodeling of repolarization via change in the expression and function of multiple ionic currents and gap junctions. Moreover, angiotensin II is important in the transduction altered myocardial stretch to remodeling of ionic currents and gap junctions. It is likely that other mechanisms are also involved in regulating primary electrical remodeling, and this is an active area of investigation. The molecular mechanisms driving remodeling of ionic currents and gap junctions in cardiac memory remain unclear. However, recently it was shown that the remodeling of KChIP2 (accessory subunit of I_{to} and $I_{Ca,L}$) in cardiac memory was mediated through the transcription factor CREB [31]. Furthermore, CREB expression is modulated by both angiotensin II binding to the AT1 receptor and by the intracellular actions of Ca^{2+} [31]. Finally, this likely explains why treatment with both angiotensin receptor and L-type Ca^{2+} channel antagonists attenuate the development of cardiac memory. Future studies that examine ionic remodeling and calcium handling remodeling in regions after primary electrical remodeling will provide important insights into common molecular mechanisms.

Secondary electrical modeling

One of the most devastating manifestations of cardiovascular disease (i.e. HF, myocardial infarction, etc.) is SCD secondary to fatal arrhythmias. The mechanisms responsible for these arrhythmias are complex and involve electrical remodeling of the myocardium in response to a structural insult, referred to as secondary electrical remodeling (Figure 2). In particular, secondary electrical remodeling involves alterations of numerous ion channels, excitation-contraction (EC)-coupling (i.e. altered sarcoplasmic reticulum [SR] Ca^{2+} cycling), and intercellular gap junctions. One of the hallmarks of secondary electrical remodeling is repolarization abnormalities, specifically a prolongation of action potential duration (APD). The ionic mechanisms responsible for remodeling of the cardiac action potential involve a complex interplay between altered outward K^+ currents (I_k), inward Ca^{2+} currents (I_{Ca}) and the late component of the inward Na^+ current (I_{Na}). In addition to altered current densities, the spatial distribution of I_K, I_{Ca} and I_{Na}, are altered, most notably in HF. These changes markedly alter normal repolarization gradients in the heart and can contribute to the development of abnormal heart rhythms (arrhythmogenesis) [32]. It is important to note that secondary electrical remodeling is not only isolated to ventricular myocytes but is frequently seen in Purkinje cells and atrial myocardium. In fact, electrical remodeling of Purkinje cells is believed to produce a substrate that is particularly prone to the development of triggered ventricular arrhythmias [33]. Additionally, electrical remodeling of atrial myocytes increases susceptibility to atrial arrhythmias such as atrial fibrillation [34].

Similar to primary electrical remodeling, down-regulation of I_{to} is one of the most reproducible events during secondary electrical remodeling in the ventricle [35]. The primary effect of diminished I_{to} on the action potential (AP) is a slowing of early repolarization, primarily changing the shape of the AP with variable effect on APD. In contrast, the delayed rectifier K^+ currents (i.e. I_{Kr}, and I_{Ks}) are largely responsible for phase 3 repolarization in cardiomyocytes. In secondary electrical remodeling, changes in I_{K1} I_{Kr}, and I_{Ks} are variable and seem to be related to the underlying cause of electrical remodeling (i.e. ischemic vs. non-ischemic cardiomyopathy) [36]. Recently, it was shown that altered expression of microRNAs might explain some of the I_K changes seen in secondary remodeling [37,38]. In particular, miR-133 expression was shown to be increased in the diabetic heart. Importantly, it was as shown that miR-133 acts to inhibit translation of HERG (subunit of I_{Kr}) [37]. In a separate study, miR-1 expression was increased in the infracted heart, causing inhibition of Kir2.1 (subunit of I_{K1}) [38]. These microRNAs represent exciting new therapeutic targets in the management of secondary remodeling and its associated arrhythmic risk.

Pharmacological blockade of I_K has shown limited promise in the management of arrhythmic risk in secondary electrical remodeling. In contrast, exciting new preclinical trials have shown promise for gene therapies targeting I_K in secondary remodeling. In a porcine model, focal gene transfer in the border zone of myocardial infarction to silence I_{Kr} has been shown to abolish ventricular arrhythmias [39]. Moreover, overexpression of mir-1 and miR-133 has been shown to decrease the risk of arrhythmias in models of diabetes and myocardial infarction, respectively [37,38].

Increasing evidence demonstrates that increased $I_{Ca,L}$ density is an important mechanism for APD prolongation in mild to moderate hypertrophy [40]. However, in severe hypertrophy and HF, $I_{Ca\text{-}L}$ is unchanged or decreased compared to control, highlighting the complexity of APD prolongation in HF. The most common alteration of $I_{Ca,L}$ in HF is delayed $I_{Ca,L}$ inactivation, secondary to diminished Ca^{2+}-dependent inactivation. For example, the amount of Ca^{2+} released from the sarcoplasmic reticulum is diminished in HF, which results in diminished Ca^{2+}-dependent $I_{Ca,L}$ inactivation. Also, Wang *et al.* [41] recently demonstrated

that the slowed $I_{Ca,L}$ inactivation in HF requires Ca^{2+}-calmodulin-dependent kinase (CAMKII). Interestingly, animal models of HF have enhanced/re-expression of fetal T-type Ca^{2+} current ($I_{Ca,T}$). It is postulated that $I_{Ca,T}$ might enhance cardiac automaticity in HF [42,43]. Unfortunately, clinical trials investigating the use of L-type Ca^{2+} channel antagonists in humans have failed to show a mortality benefit or reversal of secondary electrical remodeling [44].

Remodeling of I_{Na} is variable in HF, with reports of increased, unchanged and decreased peak I_{Na} [34]. These changes have very little impact on APD; rather, they primarily alter conduction velocity. In contrast, the late component of the $I_{Na,L}$, which accounts for only 1% of peak I_{Na}, is increased in HF. Importantly, increased $I_{Na,L}$ (as occurs in patients with Long QT Syndrome Type III) can increase APD in HF, contributing to arrhythmogenesis in HF. Therapies targeted at blocking $I_{Na,L}$ have shown promise in the management of secondary remodeling, and this is an active area of investigation [45,46].

The sodium-calcium exchanger (NCX) is an electrogenic, bidirectional transporter (moving three Na+ ions across the membrane in exchange for one Ca^{2+} ion). In mild to moderate hypertrophy, NCX expression is increased, but I_{NCX} is decreased. Increased NCX expression in hypertrophy is hypothesized to be mediated by calcineurin [47] and altered targeting of NCX to the sarcolemma is postulated to cause decreased I_{NCX}. By contrast, NCX expression and function are increased in HF and have been linked to the development of delayed afterdepolarizations (DADs) and triggered ventricular arrhythmias [48]. The role of pharmacological blockade of NCX in the management of secondary electrical remodeling is unknown because there are no I_{NCX} blockers available for clinical use at this time. Preclinical investigation of the selective NCX blocker SEA-0400 has shown mixed results in the management of secondary electrical remodeling [49].

Abnormal Ca^{2+} handling is a hallmark of altered EC coupling in secondary electrical remodeling, resulting in decreased contractile force, impaired relaxation and increased susceptibility to ventricular arrhythmias. Impaired sarcoplasmic reticulum (SR) Ca^{2+} release is caused by impaired gating properties of the ryanodine receptor (RyR) complex, with variable alteration in RyR protein expression [50]. The exact mechanisms underlying abnormal RyR Ca^{2+} are complex and likely involve multiple pathways. For example, hyperphosphorylation of RyR causes a loss of FKBP12.6-RyR binding, which has been shown to increase RyR Ca^{2+} leak [51]. Both CAMKII and cAMP-dependent kinase (PKA) phosphorylate the RyR, yet, there remains debate over which is the predominant pathway mediating RyR leak in secondary electrical remodeling [51–55]. Additionally, other mechanisms, such as oxidative stress and altered S-nitrosylation of the RyR, have been implicated in enhanced RyR Ca^{2+} leak [56,57]. For example, reduced S-nitrosylation of the RyR enhances diastolic calcium sparks in isolated myocytes. However, the mechanisms responsible for this observation are controversial. Whether enhanced RyR Ca^{2+} leak or diastolic calcium sparks in isolated myocytes translate to arrhythmogenesis in the intact heart is an active area of investigation. Spontaneous diastolic SR Ca^{2+} release in the intact heart can cause DAD's via I_{NCX}. Importantly, abnormal RyR release properties have been linked to DADs and triggered ventricular arrhythmias [58]. However, in isolation enhanced RyR Ca^{2+} leak is unlikely to be sufficient to produce arrhythmias in the intact heart. Increasing evidence indicates increased SR Ca^{2+}loading is necessary for enhanced RyR Ca^{2+} leak to produce arrhythmias [59].

Impaired SR Ca2+ reuptake is a common finding in secondary electrical remodeling and is related to decreased sarcoplasmic reticulum Ca(2+) ATPase (SERCA2a) expression and function [60]. Also, decreased phosphorylation of phospholamban (PLB) secondary to reduced β-adrenergic sensitivity enhances PLB inhibition of SERCA2a. There is increasing

evidence that decreased SERCA2a expression and/or function enhances arrhythmic risk [61–63]. In particular, our laboratory recently showed that SERCA2a expression is an important mechanism in the development of arrhythmogenic cardiac alternans. Moreover, increasing SERCA2a expression suppresses cardiac alternans and reduces arrhythmia susceptibility.

Therapies targeting abnormal SR Ca^{2+} handling are not currently available in clinical practice. However, preclinical trials have shown promise for therapies targeting RyR and SERCA2a function [64,65]. Because abnormalities in EC-coupling increase both arrhythmic risk and cause contractile dysfunction targeting these abnormalities has great potential to ameliorate the effects of both structural and electrical remodeling.

Gap junctions provide low-resistance electrical coupling between adjacent cardiac myocytes and allow movement of ions and small molecules between cells. The intercellular channel of gap junctions is composed of two hemi-channel connexons that are each composed of six connexin protein subunits. Connexin 43, the major subtype of connexin in the ventricular, exhibits heterogeneous expression throughout the heart. These heterogeneities are important in defining differences regional electrophysiological properties within the heart [66]. Importantly, remodeling of gap junctions has been demonstrated in multiple models secondary electrical remodeling and has been linked to arrhythmic risk [67–70]. In HF, both lateralization and decreased expression of connexin43 (Cx43), the major subtype of connexin in the ventricle, have been described. Decreased expression and lateralization of Cx43 decreases conduction velocity and increases dispersion of repolarization, both of which provide the substrate for arrhythmias. Therapies targeting gap junctions are an active area of investigation but have not yet reached clinical testing. However, in preclinical testing rotigaptide, a peptide designed to enhance gap junction conduction, was shown to reduce susceptibility to arrhythmogenic cardiac alternans [71]. These observations highlight the potential for therapies targeting gap junction remodeling.

Concluding remarks

Electrical remodeling of the heart occurs in response to both functional (i.e. altered electrical activation) and structural (i.e. HF, myocardial infarction, etc.) stressors. These electrophysiological changes produce a substrate that is vulnerable to malignant ventricular arrhythmias. Understanding the cellular and molecular mechanisms of electrical remodeling is important in elucidating potential therapeutic targets designed to alter maladaptive electrical remodeling. The development of such therapies could revolutionize the management of malignant arrhythmias.

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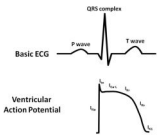

Figure 1. Example of basic electrocardiogram (ECG) and ventricular action potential

Top Panel: The ECG is a graphical representation of a coordinated sequence of electrical events in the heart during each heart beat. Atrial depolarization produces the P wave, while ventricular depolarization and repolarization produced the QRS complex and T wave, respectively. Bottom Panel: The ventricular action potential consists of an interplay of depolarizing and repolarizing currents. Abbreviations: I_{Na} = sodium current. $I_{Ca\text{-}L}$ = L-type Ca^{2+} current. I_{to} = transient outward K^+ current. I_{Kr} = rapid component of the delay rectifier K^+ current. I_{Ks} = slow component of the delayed rectifier K^+ current. I_{K1} = inward rectifier K^+ current.

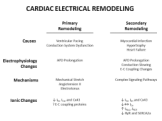

Figure 2. Schematic of primary and secondary remodeling

Abbreviations: $I_{Na\text{-}L}$ = late sodium current. $I_{Ca\text{-}L}$ = L-type Ca^{2+} current. I_{to} = transient outward K^+ current. I_{Kr} = rapid component of the delay rectifier K^+ current. I_{NCX} = sodium calcium exchanger current. Cx43 = Connexin 43. SERCA2a = sarcoplasmic reticulum Ca^{2+} ATPase. RyR = ryanodine receptor.

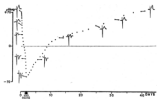

Figure 3. ECG changes in T-wave memory

Graph of T wave polarity and representative ECGs during right ventricular pacing and for 40 days post pacing. After progressive periods of pacing, progressive and persistent change in polarity of the T wave takes place. This change in T wave polarity persists for several days after the cessation of pacing. Adapted from The American Journal of Cardiology, Volume 50/Issue 2, Rosenbaum et al., Electrotonic modulation of the T wave and cardiac memory, pages 213–222, © (1982) with permission from Elsevier.