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Review

Mechanisms linking short- and long-term electrical remodeling in the heart…is it a stretch?

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Abbreviations: ECG, electrocardiogram; Na^+, sodium; K^+, potassium; Ca^{2+}, calcium; Na_V, voltage-gated sodium channel; K_V, voltage-gated potassium channel; Ca_V, voltage-gated calcium channel; I_{to}, transient outward current; I_{Kr}, rapid delayed rectifier potassium current; I_{Ks}, slow delayed rectifier potassium current; $I_{Ca,L}$, L-type calcium current; 4-AP, 4-aminopyridine; APD, action potential duration; CREB, cyclic AMP response element binding protein; NCX, sodium-calcium exchanger; Cx43, connexin 43; MRI, magnetic resonance imaging

Key words: pacing, ECG abnormalities, T wave inversion, action potential remodeling, K_V channel, Ca_V channel, Na_V channel, heart failure

Ion channels play a central role in the normal electro-mechanical functioning of the heart and are implicated in a variety of disease processes. In response to electrical or mechanical perturbations, cardiac myocytes exhibit remarkable changes in the expression and/or the function of sarcolemmal ion channels, a process that is broadly described as electrical remodeling. This remodeling has beneficial, as well as adverse, effects on myocardial function, including increased risk of fatal arrhythmias. One specific example of cardiac electrical remodeling is cardiac memory, a phenomenon induced in the heart following abnormal myocardial activation patterns produced by artificial pacemakers. Recent studies have shed new light on the molecular mechanisms underlying cardiac memory and suggest intriguing parallels between cardiac memory and heart failure. In both situations, abnormal mechanical stretch of the myocardium results in direct alterations in ion channel properties, as well as in the activation of angiotensin-dependent signaling cascades. With time, altered gene transcription and protein synthesis lead to persistent changes in ion channel levels and activities, changes that can significantly impact normal cardiac function and increase arrhythmia susceptibility.

Introduction

Changes in firing rate or activation sequence can lead to persistent alterations in the electrophysiological properties of the myocardium. This 'electrical remodeling' reflects changes in the expression and/or the function of cardiac myocyte ion channels. Although assumed to be a physiological compensatory process, electrical remodeling is also associated with cardiac dysfunction. One particularly well-studied example is atrial fibrillation,[1,2] and it is now well documented that electrical remodeling plays a role in the development and the maintenance of atrial fibrillation. In response to the mechanical and electrical changes associated with atrial rhythm disturbances, the expression and/or the properties of a number of atrial ion channels are altered and atrial refractory periods are shortened. The consequence of this remodeling is an increased propensity for atrial fibrillation, a scenario summed up in the phrase "atrial fibrillation begets atrial fibrillation."[2,3]

Considerable evidence has also accumulated demonstrating electrical remodeling in the ventricles, and the pathophysiological consequences of this remodeling can be profound, including an increased risk of developing life-threatening ventricular arrhythmias. Although the underlying mechanisms involved in ventricular electrical remodeling are less well understood than those in the atria, progress has been made recently in studies of cardiac memory, one form of ventricular ion channel remodeling. The term "cardiac memory" was originally coined to describe the persistent changes observed in the surface electrocardiogram (ECG) that result from abnormal activation sequence, typically produced by pacing. The experimental observation is that the heart retains a "memory" of the prior activation rate or sequence and continues to exhibit changes even after the abnormal activation pattern has been restored to normal. Recent insights gleaned from investigations into the mechanism involved in cardiac memory suggest parallels with several other examples of long-term ventricular electrical remodeling, which is evident in a variety of myocardial disease states, including ventricular hypertrophy, ischemia and heart failure.[4] It seems increasingly clear that, at the heart of both mechanisms, lies a complex array of changes in ion channel expression levels and properties.

Cardiac Memory

The hallmark of cardiac memory is a persistent alteration in the pattern of myocardial repolarization as a consequence of changes in the pattern of myocardial activation. This change in repolarization is manifest as an alteration in the T wave of the surface ECG, specifically, an inversion of normally upright T waves. The

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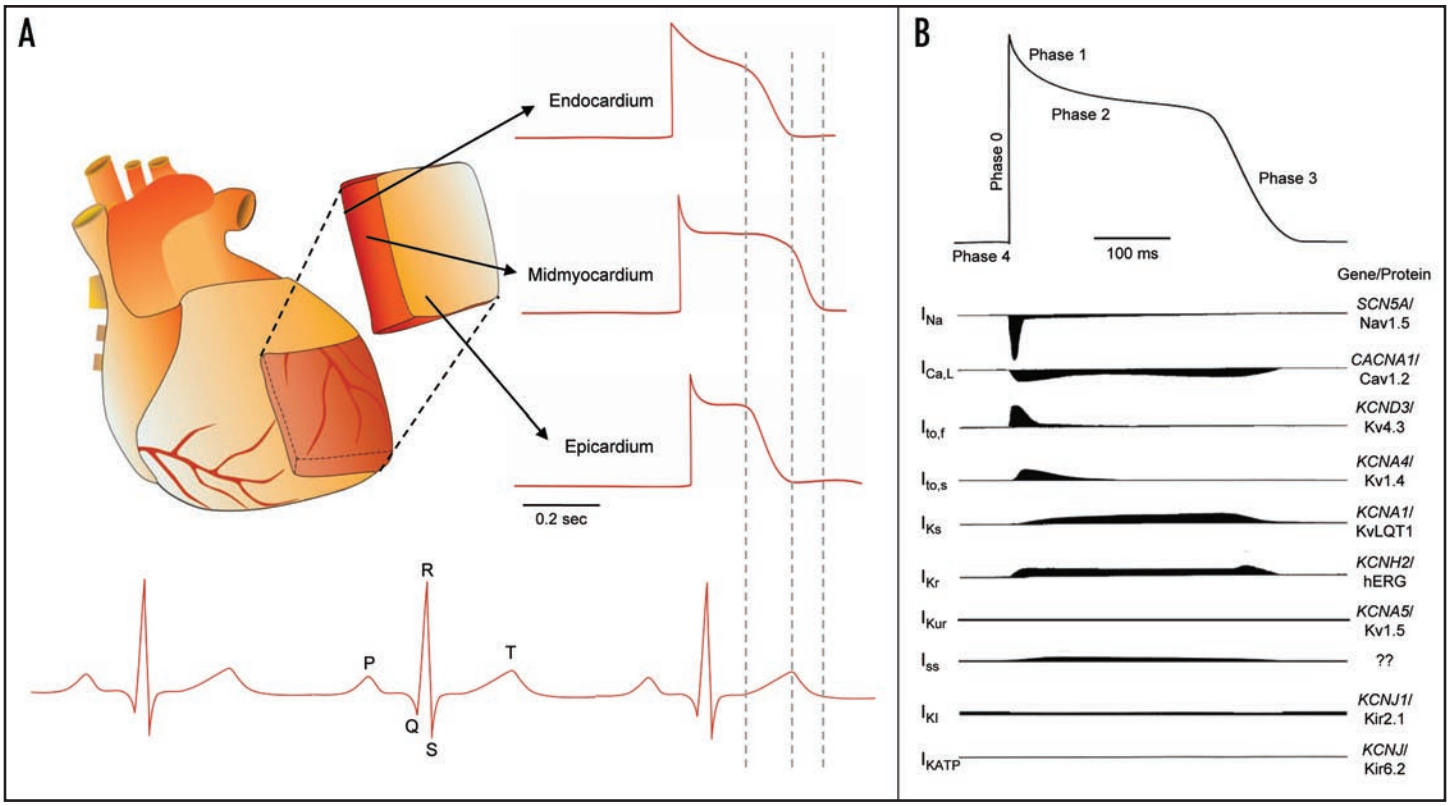

Figure 1. Electrical activity in the ventricular myocardium. (A) Schematic of a human heart with a ventricular wedge removed and representative action potential waveforms recorded in different regions of the ventricular wall. In the lower panel is a schematic of a surface electrocardiogram; three sequential beats are displayed. (B) Schematized ventricular action potential waveform and underlying ionic currents. The waveforms of the voltage-gated inward Na^+ (Na_V) and Ca^{2+} (Ca_V) currents and the multiple types of K^+ (K_V and K_{ir}) currents contributing to ventricular action potential repolarization are illustrated. There are multiple K_V currents expressed in ventricular myocytes and the properties of these currents are distinct.

finding that cardiac pacing results in persistent T wave inversion was originally described by Chatterjee in 1969.[5] Subsequent studies by Rosenbaum and colleagues, and more recently by Wecke and colleagues, have delineated many of the basic features of the phenomenon of cardiac memory.[6-8]

The onset of cardiac memory is rapid; as little as 15 minutes of pacing results in T wave changes. In humans, continuous pacing for approximately one week results in a steady state change in the T waves. After cessation of pacing, cardiac memory dissipates at a rate that depends on both the duration of prior pacing and the amount of continued pacing. Importantly, cardiac memory exhibits *accumulation*, namely, the duration and the degree of the T wave abnormalities observed are dependent on the duration and degree of abnormal activation. Intriguingly, accumulation occurs even in the absence of overt T wave changes. Both Rosenbaum and colleagues and del Balzo and colleagues[6,9] demonstrated that multiple trains of pacing stimuli resulted in progressively more cardiac memory, even when enough time was left between trains for apparently complete resolution of the alterations in T wave morphology. This observation suggests that the changes observed in the T wave in cardiac memory do not provide an accurate reflection of the underlying pacing-induced electrical changes that have transpired in the ventricular myocardium.

The fundamental features of cardiac memory are reminiscent of those associated with learning and memory in the nervous system and, indeed, these similarities actually led to the introduction of the term cardiac memory by Rosenbaum.[6] In an additional parallel, cardiac memory also appears to exhibit both short-term and long-term forms, with the latter being directly dependent on protein synthesis.[10] This distinction between short and long-term memory is potentially useful when considering the underlying mechanisms.

Generation and Propagation of Ventricular Action Potentials

Myocardial electrical activity is initiated in pacemaker cells in the sinoatrial node and is propagated through the atria to the atrioventricular node. After a brief pause, activity spreads in the conducting Purkinje fibers to the apex of the heart and into the working, ventricular myocardium. In cells in each of these specialized regions, excitation results in action potential generation, followed by relaxation and a period of refractoriness until the next impulse is generated and propagated. The generation of myocardial action potentials reflects the sequential activation and inactivation of ion channels that conduct depolarizing, inward (Na^+ and Ca^{2+}), and repolarizing, outward (K^+), currents (Fig. 1B). The propagation of activity through the myocardium and the coordination of the electromechanical functioning of the ventricles also depend on electrical coupling between cells, mediated by gap junctions. The normal coordinated electrical activity of the whole heart is readily detected in the surface ECG (Fig. 1A).

In ventricular myocytes, the upstroke of the action potential (Phase 0) is rapid, resulting from the activation of voltage-gated Na^+ (Na_V) channels (Fig. 1B). Phase 0 is followed by a transient repolarization (Phase 1), reflecting Na_V channel inactivation and

the activation of the voltage-gated transient outward K^+ current, I_{to} (Fig. 1B). This transient repolarization or Phase 1 "notch" influences both the height and the duration of the plateau (Phase 2) of ventricular action potentials. Membrane depolarization also activates voltage-gated Ca^{2+} (Ca_V) currents, and the influx of Ca^{2+} through L-type Ca_V channels during the phase 2 plateau is the main trigger for excitation-contraction coupling in the working ventricular myocardium.[11] The driving force for K^+ efflux is high during the plateau Phase and, as Ca_V channels inactivate, outward K^+ currents predominate, resulting in (Phase 3) repolarization, bringing the membrane voltage back to the resting potential (Fig. 1B). In contrast to Na_V and Ca_V currents, there are multiple types of voltage-gated K^+ (K_V) currents, as well as non-voltage-gated, inwardly rectifying K^+ (K_{ir}) currents that contribute to ventricular action potential repolarization. The greatest functional diversity is among K_V channels (Fig. 1B). At least two types of transient outward currents, $I_{to,f}$ and $I_{to,s}$, and several components of delayed rectification, including I_{Kr} ($I_{K(rapid)}$), I_{Ks} ($I_{K(slow)}$) and I_{Kp}, for example, have been distinguished in ventricular myocytes (Fig. 1B). A large number of ion channel pore-forming and accessory subunits that encode Na_V, Ca_V, K_V and K_{ir} channels have been identified,[12] and considerable progress has been made in identifying the pore-forming (α) subunits encoding the various types of (Na^+, Ca^{2+} and K^+) ion channels expressed in ventricular myocytes. The *SCNA5* locus, for example, encodes the predominant Na_V channel α subunit expressed in the ventricular myocardium, $Na_V1.5$, and *CACNA1C* encodes the $Ca_V1.2$ protein, the pore-forming subunit of L-type ventricular Ca_V channels (Fig. 1B). Molecular physiological studies have also revealed that multiple K_V and Kir channel α subunits are expressed in the ventricular myocardium and, in addition, that the various (K_V and K_{ir}) subunits encode functionally distinct ventricular K_V and K_{ir} currents[12] (Fig. 1B).

Electrophysiological studies suggest that the waveforms of action potentials in myocytes in different regions of the ventricles are distinct (Fig. 1A). These differences contribute to the normal unidirectional propagation of excitation through the myocardium and to the generation of normal cardiac rhythms. The observed heterogeneity in action potential waveforms in different ventricular cell types (Fig. 1A) reflects differences in ion channel expression levels, and modeling studies suggest that small changes in the time- and/or voltage-dependent properties of cardiac sarcolemmal ion channels can have rather profound effects on action potential durations, as well as impact refractoriness and rhythmicity.[12]

Ion Channel Remodeling in Short-Term Cardiac Memory

Alterations in the functional cell surface expression and/or the properties of ventricular myocyte ion channels must underlie the repolarization changes and the resulting T wave abnormalities manifest in cardiac memory. Nevertheless, the molecular details of the remodeling and the underlying mechanisms responsible for short-term cardiac memory remain poorly understood. In studies on the intact canine heart, it has been shown that the K^+ channel blocker 4-aminopyridine (4-AP) inhibits the formation of cardiac memory, whereas the Na_V channel blocker lidocaine has no effect.[9] In canine tissue, the Ca_V channel blocker nifedipine also inhibits memory formation, but the beta adrenergic blocker propanolol has no effect on cardiac memory.[13] In a study of human short-term memory, Lee and colleagues[14] reported that both lidocaine (Na_V channel blocker) and verapamil (another Ca_V channel blocker) inhibited the induction of short-term memory.

It was further noted that cardiac memory resulted in attenuation of the Phase 1 notch of the action potential, which is determined largely by the transient outward K_V current, I_{to} (Fig. 1B); additionally, I_{to} is sensitive to 4-AP.[15] Pursuing the hypothesis that stretch-activated angiotensin II release occurs in cardiac memory, Yu and colleagues[16] demonstrated that application of angiotensin II to epicardial myocytes resulted in a marked reduction in I_{to} density, a shift in current activation to more depolarized potentials, and a slowing of recovery from inactivation, all of which resulted in an electrical phenotype (in epicardial cells) more similar to endocardial cells. No changes in the expression levels of the transcripts encoding the $K_V4.3$ (*KCND3*) or $K_V1.4$ (*KCNA4*) subunits which encode I_{to} channels (Fig. 1B), however, accompanied these electrical changes. Interestingly, it has also been reported that the angiotensin receptor interacts directly with $K_V4.3$ and modulates the gating and internalization of $K_V4.3$-encoded I_{to} channels.[17]

Taken together, these findings indicate a role for post-translational remodeling of Ca_V and K_V channels (possibly regulated through angiotensin) in short-term cardiac memory (Fig. 2), with the additional involvement of Na_V channel remodeling in human ventricles.

Ion Channel Remodeling in Long-Term Cardiac Memory

Similar to short-term memory, attention in studies of long-term cardiac memory has also focused on the remodeling of I_{to}, which underlies the Phase 1 action potential notch and is particularly prominent in the epicardium.[18] Yu and colleagues,[19] for example, reported a positive shift in activation and slowed recovery from inactivation in epicardial I_{to} after induction of cardiac memory in the canine heart. In addition, $K_V4.3$ (*KCND3*) mRNA levels were reduced, which would be expected to further reduce I_{to}. In addition, it was reported by Plotnikov and colleagues[20] that neonatal canine hearts exhibit neither cardiac memory nor I_{to} and, in addition, that the capacity to induce cardiac memory parallels the developmental expression of I_{to}. In a study of other repolarizing, ventricular K^+ currents (notably I_{Kr} and I_{Ks}), Obreztchikova and colleagues[21] examined tissue slices from the canine heart after induction of cardiac memory. They reported changes in I_{Kr} density and shifts in the voltage-dependence of channel activation, such that the normal transmural gradient (with greater epicardial than endocardial current at baseline) was reversed. In addition, epicardial I_{Ks} exhibited a shift in activation voltage without a significant change in the transmural current density gradient. In addition, Plotnikov and colleagues[13] reported that cardiac memory in adult canine ventricles is inhibited by amlodipine (a blocker of L-type Ca^{2+} ($I_{Ca,L}$) channels) and that induction of memory is associated with a positive shift in activation and a slowing of inactivation of $I_{Ca,L}$ in epicardial myocytes, an effect that would be expected to increase $I_{Ca,L}$ in vivo.

Cardiac myocytes are extensively connected through low resistance gap junctions, and (electrical) coupling via gap junctions is a key feature of myocardial electrical activity. In the ventricles, the main gap junction protein expressed is connexin 43 (Cx43).[22] The remodeling of gap junctions in long-term cardiac memory was examined by Patel et al.[23] By recording from multiple sites in the intact dog heart, they found a slowing of conduction velocity after induction of

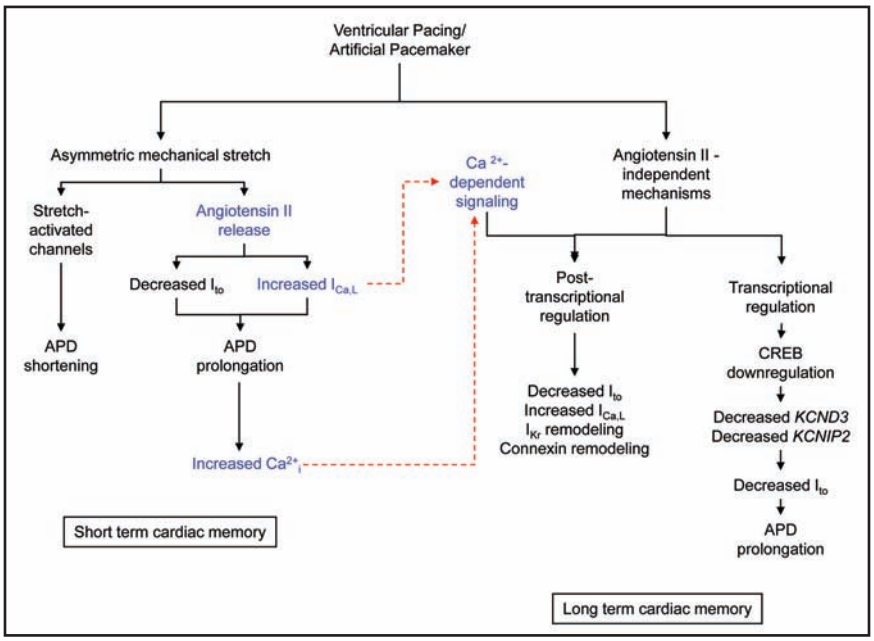

Figure 2. Proposed models of short and long term cardiac memory. A summary of proposed mechanisms involved in remodeling in cardiac memory is illustrated. Key signaling components are indicated in blue and are arranged based on their known involvement in short term or long term memory, with hypothesized connections between the two mechanisms through increased intracellular Ca^{2+} (Ca^{2+}_i) highlighted with the red dotted lines (see text for further details).

cardiac memory. Immunohistochemical staining for Cx43 revealed marked redistribution of gap junctions from the intercalated disks at the ends of the myocytes to a more random distribution along the length of the myocytes. Interestingly, this change was evident only in the epicardial layer near the pacing electrode. Long-term cardiac memory, therefore, appears to involve changes in several K_V currents (I_{to} and I_{Kr}), as well as $I_{Ca,L}$, in addition to changes in electrical coupling through gap junction channels.

Heterogeneities in Ion Channel Remodeling

As discussed above, the morphologies of ventricular action potentials derive directly from the behavior of the various sarcolemmal ion channels. However, the relationship is a complex one in cardiac tissue due to heterogeneities in both the types and the densities of the various ion channels expressed in different regions of the myocardium.[22] Most notably, distinct action potential waveforms have been recorded at different depths of the ventricular wall (Fig. 1) with a resultant gradient in the time of repolarization, a feature described as "transmural dispersion of repolarization."[18] Heterogeneities in ventricular action potential waveforms are clearly evident in dissociated cell studies. Electrotonic coupling through gap junctions, however, plays an important role in regulating the normal spread of electrical activity in the intact ventricular myocardium in vivo, a feature that is difficult (or impossible) to capture in studies of dissociated cells. The degree to which cell-cell coupling attenuates electrical gradients in the intact heart remains an area of active investigation. Nevertheless, in light of this consideration, studies which are performed in either intact hearts or in large tissue wedges are more likely to reflect the in vivo situation and warrant closer examination.

The ion channel remodeling described above in both short-term and long-term cardiac memory is expected to result in ventricular action potential prolongation due to the attenuation of repolarizing K^+ currents. Perhaps not surprisingly, the data proves more complicated. Costard-Jackle and colleagues, for example, studied short-term cardiac memory in the isolated Langendorff-perfused rabbit heart by recording from the epicardial surface during both atrial and right ventricular endocardial pacing.[24] In these studies, they found that, at baseline, there was an inverse relationship between the action potential duration and the time of activation for each point on the epicardium, a situation that intuitively makes sense as a mechanism of homogenizing the time of repolarization throughout the ventricles. With ventricular pacing, this inverse relationship was initially absent but was re-established over the course of 60–120 minutes of continuous pacing. Importantly, this experimental observation requires both the prolongation and the shortening of action potentials, albeit in different regions of the ventricles.

A similar study was performed by Janse and colleagues[25] in the intact canine heart. In vivo epicardial pacing was performed on anesthetized dogs for two hours. Recordings were obtained from up to 98 epicardial locations and 144 intramyocardial electrodes. As in the rabbit heart, a correlation between activation time and activation-recovery interval (a correlate of action potential duration) resulted in a uniform repolarization throughout the myocardium. After induction of cardiac memory, they recorded a shortening of the activation-recovery interval, which was uniform across the ventricular wall, but exhibited apical-basal and anterior-posterior gradients. In addition, these investigators noted that monophasic action potentials also exhibited an attenuation of the Phase 1 notch at many sites.[25]

The situation is no clearer in studies of long-term memory. For example, Coronel and colleagues[26] recently reported some slowing of transmural activation and an increase in the transmural repolarization gradient in regions close to the pacing electrode, although no significant changes in epicardial action potential duration were observed. In contrast, Jeyaraj and colleagues[27] reported marked epicardial action potential prolongation in regions distant from the pacing electrode and no changes in the transmural gradient of repolarization. One consistent feature of all these studies, however, has been the finding of marked heterogeneity of the changes in action potential waveforms observed in different regions of myocardium and at different depths of the myocardial wall. Heterogeneity in remodeling, therefore, appears likely to represent a key feature of cardiac memory.

Does Ion Channel Remodeling Account for T Wave Changes?

Despite a century of clinical use, the cellular electrophysiology underlying the T wave of the surface ECG remains incompletely understood.[28] Electrical activity in the ventricles results in two major deflections on the surface ECG: the QRS complex which reflects ventricular activation; and the T wave which reflects ventricular repolarization (Fig. 1A). More precisely, both deflections

reflect the propagation of activation and repolarization wave fronts through the complex three dimensional structure of the ventricles. Normally, the QRS complex and T wave exhibit a similar spatial axis despite the opposite polarity of the wave fronts. It is, therefore, implied that the pattern of propagation of repolarization is *not* the same as the pattern of activation. Rather, heterogeneities in action potential duration result in the propagation of repolarization in a direction that is opposite to that of the depolarization wavefront (Fig. 1). Specifically, it appears that depolarization proceeds from endocardium to epicardium, whereas repolarization proceeds from epicardium to endocardium (i.e., action potential duration is shorter in the epicardium than the endocardium). As mentioned above, this feature is referred to as "transmural dispersion of repolarization" and plays a key role in arrhythmogenesis.[28] Although the transmural gradient is demonstrated clearly in experimental models, it remains unclear whether these gradients are attenuated in vivo by cell-cell coupling via gap junctions.[22] In addition, the possible contributions of other heterogeneities in myocardial electrical and/or structural properties to the pattern of action potential propagation remains poorly understood.

Based on the experimental observations, it is expected that the inverted T waves evident in cardiac memory reflect a change in the repolarization gradient, although whether transmural gradients or gradients between different regions are the primary determinants of the change in repolarization sequence is not clear. Although the results are not entirely consistent, two recent studies have shed some light on the origin of the altered repolarization gradient in cardiac memory. As discussed above, Jeyaraj and colleagues[27] found no change in the transmural gradient of repolarization but a new gradient between anterior and posterior regions of the heart whereas Coronel and colleagues[26] identified a new transmural gradient of repolarization in some regions of the ventricles. Clearly, further experiments are needed to clarify this important feature of cardiac memory.

Role of Signaling Mechanisms in Remodeling

The mechanisms linking abnormal electrical activity to ion channel remodeling in cardiac memory remain only partially understood. Interestingly, altered cardiac electrical activation also changes the mechanical properties of the heart, raising the possibility that alterations in mechanics contribute directly to the evolution of cardiac memory. A recent paper by Sosunov and colleagues[29] examined this possibility in the Langendorff-perfused rabbit heart. These investigators directly manipulated ventricular stretch by: (a) removing ventricular mechanical loading by shunting the ventricles to the bath; (b) increasing ventricular load with inflatable catheters; and (c) uncoupling excitation and contraction with blebbistatin.[30] All of these interventions led to the common conclusion that increased wall stretch enhanced the development of cardiac memory, while reduced load attenuated cardiac memory. In addition, Sosunov and colleagues[29] reported that directly stretching at a single point on the myocardium induced T wave changes similar to cardiac memory. This observation clearly supports the hypothesis that altered mechanical activity, rather than electrical patterns per se, is a key determinant of cardiac memory. Jeyaraj and collaborators[27] also recently completed studies focused on examining the possible role of mechanoelectrical feedback in long-term cardiac memory. Studying intact canine hearts using optical action potential imaging and tagged magnetic resonance imaging (MRI) techniques, these investigators found that the regions of most marked action potential prolongation were distant from the pacing electrode and located in regions of the greatest tissue strain. Taken together, the results presented in these two recent papers[27,29] highlight a possible role for tissue deformation, through mechanical stretch, rather than electrical activity per se, as the inciting event in the formation of cardiac memory.

Myocardial stretch is known to result in the local release of angiotensin, as well as activation of immediate early genes,[31,32] leading to the hypothesis that local angiotensin release could play a role in cardiac memory. Ricard and colleagues[33] examined this hypothesis in intact canine hearts and demonstrated that short-term cardiac memory was inhibited by the application of saralasin (a selective angiotensin II receptor blocker), captopril (an angiotensin converting enzyme inhibitor), and chymostatin (a cystein protease inhibitor). In particular, the efficacy of chymostatin suggests that local paracrine angiotensin II plays a role, rather than circulating angiotensin II. Patberg and colleagues[34] examined the role of the CREB (cAMP response element binding protein) transcription factor and found that short-term cardiac memory was associated with a marked reduction in the level of nuclear CREB, with the greatest effect in the region (cells) closest to the site of pacing.

By analogy with short-term and long-term neuronal memory, it has been hypothesized that the evolution of long-term cardiac memory may be a protein-synthesis dependent process. This hypothesis was supported by the results of Shvilkin and colleagues[10] who demonstrated that long-term cardiac memory was partially inhibited by the protein synthesis inhibitor cycloheximide. In addition, Patberg and colleagues,[34] in studies focused on examining the role of the CREB transcription factor, reported that long-term cardiac memory resulted in reduced CREB binding to CRE (i.e., the CREB sensitive promoter sequence) and specifically reduced the binding of the CREB protein to the *KCND3* ($K_V4.3$) CRE sequence.[34] These results suggest that reduced transcription of CRE-sensitive elements (such as in *KCND3*) may contribute to long-term cardiac memory.

Does Cardiac Memory Reflect Stretch-Induced Remodeling?

The recent data from both Jeyaraj and colleagues and Sosunov and colleagues[27,29] draws new attention to the role of stretch in the initiation of cardiac memory (Fig. 2). It is well established that cardiac myocytes have a complex and extensive response to mechanical stimuli (reviewed by Sadoshima and Izumo[35]). One important component of this mechanism still under investigation concerns the molecular identity of the stretch sensor; possible candidates include direct regulation of ion channels, linkages with integrins, and regulation by membrane bound receptor tyrosine kinases. Stretch induced responses can be loosely grouped into immediate responses, typically via direct activation of ion channels, and delayed responses, which involve the activation of signaling cascades.

A wide variety of stretch sensitive receptors are known to exist on cardiac myocytes, including non-selective cation channels, K^+ channels and chloride (Cl^-) channels. In addition, mechanical regulation of cardiac ion channels, which are traditionally defined as voltage- or ligand-gated channels, has been demonstrated for ATP sensitive K^+ channels, delayed rectifier K^+ channels, the Na/K exchanger, and L-type Ca^{2+} channels.[36,37] The electrophysiological effects of stretch-mediated channel activity will be dependent on the

membrane potential and other current activity. In general, however, it has been found that stretch results in: (a) depolarization of the resting membrane potential; (b) action potential shortening; and (c) reduction in action potential plateau voltage.[36] These effects are linked largely to the activity of stretch activated non-selective cation channels.[36] Recalling that the cardiac regions in short-term memory with the greatest tissue deformation display action potential shortening raises the interesting question of whether this reflects the activation of a local population of stretch activated ion channels.

Mechanical stretch also activates a wide array of signaling cascades, including immediate early genes (e.g., *c-fos*, *c-jun*, *Egr-1* and others), intracellular second messenger pathways (e.g., phospholipases, tyrosine kinases, mitogen-activated protein kinases, protein kinase C and others), and activation of various growth factor pathways (e.g., angiotensin II, endothelin-1, basic fibroblast growth factor, and others). Many, although not all, of these effects appear to be mediated through activation of angiotensin II.[35] Interestingly, dissociated cardiac myocytes exposed to electrical currents to mimic pacing exhibit hypertrophy, and this hypertrophy is reportedly dependent on cellular release of basic fibroblast growth factor.[38] This array of signaling and regulatory pathways likely contributes to the response to long-term pacing. Although angiotensin II appears to play an important role, the role of other systems and of the downstream elements remains to be elucidated.

Summary Model of Cardiac Memory

Although incomplete, the current data on cardiac memory suggest the model illustrated in Figure 2. In short-term memory, mechanical strain results in direct activation of stretch-activated ion channels and release of angiotensin. The latter (release of angiotensin) then results in decreased I_{to} and increased $I_{Ca,L}$, which in turn, may activate other Ca^{2+}-dependent signaling. One possible scenario is that the enhanced Ca^{2+} influx of short-term memory leads to the signaling cascades of long-term memory (a possibility emphasized by the red dotted line in Fig. 2). Alternatively, the mechanisms of short- and long-term memory may function in parallel, with no direct dependence of long-term memory on the previous generation of short-term memory. Long-term memory appears to operate, at least in part, through angiotensin-independent pathways to regulate gene transcription with resulting changes in ion channel gene expression. Specifically, altered CREB regulated transcription results in decreased expression of *KCND3* ($K_V4.3$) and *KCNIP2* (KChIP2), and secondarily to decreased I_{to}. Regulation of genes encoding other ion channel subunits or regulatory proteins will lead to alterations in the functional expression of other K^+ channels as well as Ca^{2+} channels and gap junctions, and to further electrical remodeling.

Cardiac Memory and Heart Failure Remodeling

The structural and electrical remodeling which occurs in heart failure is the subject of extensive literature.[4,39,40] However, some pertinent parallels with the recent studies of cardiac memory have emerged. Although the term "heart failure" encompasses multiple pathophysiologic mechanisms, several common features have been identified. Typically, for example, ventricular action potential durations are reported to be prolonged due to downregulation of K^+ currents, notably I_{to}. In addition, Na/K ATPase function is reduced, with consequent: (a) action potential prolongation; and (b) increased intracellular Na^+ and resultant enhanced sodium-calcium exchange (NCX)-mediated Ca^{2+} influx. Connexin 43 dysregulation is frequently associated with alterations in the subcellular localization of gap junctions. Perhaps most importantly, several changes in Ca^{2+} handling are evident in heart failure, including defective sarcoplasmic reticulum sequestration of Ca^{2+} and increased NCX activity (potentially as a compensatory mechanism). The net effect of these changes is a depletion of Ca^{2+} stores, slowed relaxation of systolic Ca^{2+} transients, and increased diastolic Ca^{2+} levels. An emerging understanding of heart failure is that global dilation of the heart results in increased stretch of the myocardium. In turn, this dilation/stretch activates remodeling pathways to compensate for this mechanically adverse situation. Given the parallels that can be identified between cardiac memory and heart failure, it appears likely that cardiac memory reflects a similar mechanism, albeit expressed only in one region rather than globally.

The Purpose of Remodeling

In a quote attributed to J.B.S. Haldane, "Teleology is like a mistress to the biologist; he dare not be seen with her in public but cannot live without her."[41] This remark is particularly applicable to the phenomenon of remodeling. Clinically, remodeling associated with heart failure in particular ultimately leads to progressive cardiac dysfunction. As such, considerable clinical attention is directed towards preventing or reversing heart failure induced remodeling. Nonetheless, it is presumed that these (remodeling) mechanisms are designed to provide a benefit. It has been speculated that the action potential prolongation in heart failure represents remodeling that attempts to maintain contractile force.[42] Other remodeling may then represent a secondary effort to maintain normal Ca^{2+} homeostasis. Broadly speaking, the signaling pathways activated in heart failure represent a return to a more fetal genetic program, and this remodeling has been hypothesized to provide metabolic reprogramming more amenable to maintaining cardiac function in the presence of ischemia. Potentially, re-activation of a fetal genetic program(s) may also have electrophysiological consequences, such as changes in repolarizing K^+ currents or changes in gap junction expression and/or distribution, that are not beneficial, and may even be deleterious, in the context of myocardial electrical and electromechanical functioning. Overall, heart failure remodeling is postulated to represent an attempt to enhance contractile function despite deteriorating mechanical conditions. By extension, we may speculate that cardiac memory represents an attempt to normalize the mechanical function of the ventricles by selectively enhancing contractility in regions of increased strain.

Clinical Implications of Cardiac Memory

Pacemakers are implanted for the treatment of bradyarrhythmias either due to sinus node dysfunction or conduction system disease. Despite the obvious necessity of a pacemaker in these patients, it is increasingly appreciated that long-term right ventricular pacing has adverse effects with increased rates of heart failure, hospitalization and atrial fibrillation.[43,44] Although these effects may relate to the mechanical atrial-ventricular dyssynchrony, the possible clinical consequences of direct electrical effects of the pacemaker remain to be explored. One study demonstrated an apparent connection between cardiac memory and diastolic mechanical function.[45] Whether

cardiac memory represents a sign of adverse effects by pacing or is a benign feature remains to be fully defined.

It has been suggested that the electrical remodeling associated with cardiac memory may be arrhythmogenic, particularly in light of the fact that transmural dispersion of repolarization is believed to contribute to arrhythmogenesis. Case reports have demonstrated altered sensitivity to anti-arrhythmic medications and arrhythmias in patients with pacemakers.[46,47] Despite these case reports, pacing does not clinically appear to result in a substantial arrhythmia burden. In this regard, cardiac memory differs from heart failure which represents a significant risk of lethal arrhythmias. Given the similarities in molecular remodeling, the question then arises regarding why cardiac memory appears to result in fewer arrhythmias than heart failure. The explanation may again lie in a distinction between local and global processes. Ventricular arrhythmias are typically considered to require both a "trigger" to start the arrhythmia and a "substrate," a region of myocardium with heterogenous conduction properties that provides a region for a re-entrant circuit. Importantly, this circuit must be of a minimal size to support the arrhythmia. Although purely speculative, it is possible that the localized process of cardiac memory does not provide an adequate substrate for the support of arrhythmias.

Despite these considerations of possible adverse effects, cardiac memory also offers likely benefits in the management of heart failure. Heart failure represents a growing health care epidemic, with approximately 550,000 new cases each year and, especially when resulting from ischemic disease, is frequently characterized by ventricular dyssynchrony, i.e., some regions contract better than others as a result of myocardial scarring. This scenario is likely parallel to the abnormal contractile pattern induced by a pacemaker. A relatively new treatment for heart failure, cardiac resynchronization therapy (CRT), involves the placement of multiple pacemaker leads (in the right atrium, right ventricle and left ventricle) in an attempt to restore mechanical synchrony. This technique results in a degree of "reverse remodeling" with improvement in mechanical indices of cardiac function, as well as changes in gene expression.[48,49] Cardiac memory, as the manifestation of molecular and cellular effects of the pacemaker, undoubtedly plays a role in this beneficial reverse remodeling. Further study of cardiac memory might then translate into more effective use of pacemakers in the treatment of heart failure.

Future Directions

Although pacing has been frequently viewed as a purely electrical mechanism to treat bradycardia, it is becoming increasingly clear that pacing is actually a potent modulator of cellular and molecular dynamics. In addition, far from being a benign clinical curiosity, cardiac memory has emerged as an integral component of cardiac remodeling. It is increasingly appreciated that the ion channel remodeling associated with heart failure results in an arrhythmogenic milieu; although less arrhythmogenic, cardiac memory likely reflects similar processes. Further advances in understanding will likely draw on the information which is known about heart failure and stretch induced remodeling, with particular attention to the complex heterogeneity of the ventricular myocardium. In the future, it is hoped that the ion channel remodeling of cardiac memory can be harnessed as another method to treat the failing heart.

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