Cardiac memory: Mechanisms and clinical implications

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Cardiac memory (CM) is identified as an altered T wave on electrocardiogram and vectorcardiogram that is seen when sinus rhythm resumes after a period of abnormal myocardial activation. Specifically, the sinus rhythm T wave tracks the QRS vector of the abnormal impulse. CM frequently is induced by ventricular pacing or arrhythmias and historically has been considered of minor relevance to medical practice. Although it has long been known that CM can mimic the T-wave inversions of myocardial ischemia, we learned more recently that CM can alter the actions of antiarrhythmic drugs. Furthermore, it provides a template for investigating the mechanisms whereby ventricular pacing affects myocardial physiology. In this article we review the mechanisms believed responsible for induction of CM and some of its more recently recognized clinical manifestations. We also discuss the controversies regarding atrial memory and its potential clinical implications.

KEYWORDS Electrocardiography; Vectorcardiography; Ventricular repolarization

Introduction

The term remodeling is frequently used to describe adaptational and maladaptational processes whereby the heart responds to disease or external stimuli. Cardiac memory (CM) refers to a specialized form of remodeling. It is characterized by an altered T wave on electrocardiogram (ECG) or vectorcardiogram recorded during sinus rhythm (or any rhythm with normal ventricular activation) and induced by a preceding period of altered electrical activation. CM induced by pacing is shown in Figure 1. Note that by day 21, T-wave amplitude has changed in the direction of the paced QRS complex in leads I and aVF. By day 7, the T vector has moved in the direction of the paced QRS vector, and this change continues to evolve through day 21. Hence, CM accumulates over time and (although not shown in this figure) slowly resolves after pacing has stopped.1–3

Rosenbaum et al1 introduced the term cardiac memory in 1982; however, the phenomenon has been observed since the 1940s. CM has been described following stimuli such as electrical pacing, intermittent left bundle branch block, paroxysmal tachycardia, and preexcititation.2 In this article, we discuss the mechanisms underlying CM and its clinical expression.

Mechanisms of CM

Electrophysiologic changes and their underlying ion channel determinants

The electrophysiologic changes of CM have been studied in intact animal models, isolated hearts, isolated tissues, and single cells.2 Electrocardiographic changes are seen after resumption of normal ventricular activation. A good example of the altered relationship of repolarization to activation was provided by Costard-Jäckle et al.4 They transiently changed the ventricular activation pattern in Langendorff-
perfused rabbit hearts and induced repolarization changes that outlasted the pacing period.\(^4\) Resumption of atrial pacing after the heart had been paced from the right ventricle resulted in loss of the normal inverse relationship between activation time and action potential duration. The duration of loss of this relationship increased with the duration of ventricular pacing, and this was considered to be a manifestation of CM.

Intact canine studies have provided more current experimental information on CM. Minutes to hours of pacing (producing “short-term” CM) and 2 to 5 weeks of pacing (“long-term” CM) have been used. The pacing periods are an experimental convenience; there is no implication that CM accumulation is not a continuum. The long-term CM protocol does not induce myocardial hypertrophy or significant alterations in coronary flow or hemodynamics.\(^3\)

Most studies in canine heart have used left ventricular epicardial pacing to induce CM.\(^2\) In this setting (Figure 1), about 2 weeks of pacing at physiologic rates is required to achieve a steady-state change in the T wave. Resolution of these changes upon returning to sinus rhythm is slow and is influenced by the prior duration of pacing. After 2 to 3 weeks of pacing, resolution occurs in less than 1 month. After 4 to 5 weeks pacing, resolution occurs in 2 months or longer.\(^3\) These observations contrast with those noted when right ventricular endocardial pacing was used to induce CM in human heart. Here, evolution and resolution are far faster.\(^5\) Differences in protocol and pacing site (chamber and epicardial vs endocardial impulse initiation) likely account for the contrasting observations, although species variability also may be an issue. The mechanisms determining the differences in time course with endocardial and epicardial pacing are currently under investigation.

The altered T wave in short-term CM induced by left ventricular epicardial pacing was shown recently in mapping experiments on \textit{in situ} canine heart to result from an altered apicobasal rather than transmural repolarization gradient.\(^6\) \textit{In situ} mapping has not been performed in long-term CM, but studies of tissues isolated from the ventricles have shown changes in action potential configuration and specific ion channels.\(^2\) The action potential changes are most marked near the pacing site. Following left ventricular epicardial pacing, epicardial action potentials recorded 1 to 2 cm from the pacing electrode manifest a reduced phase 1 notch, an elevated plateau, and a prolonged duration. In the endocardium, the plateau also is elevated, but action potential prolongation is less marked. The result is an altered transmural repolarization gradient near the pacing electrode (Figure 2).

![Figure 1](image1.png) Evolution of cardiac memory in the canine model. **Upper panels:** Leads I and aVF before ventricular pacing (control), during pacing, and 1 hour after cessation of pacing on days 7 and 21 and after 3 days of recovery after pacing was permanently discontinued. **Bottom panel:** Frontal plane vectorcardiogram from the same animal. Cross-hairs, 0.5 × 0.5 mm. The T-wave vector during sinus rhythm is indicated by the arrow. (Adapted with permission from Yu et al.\(^12\))

![Figure 2](image2.png) Action potential characteristics and transmural left ventricular gradients in long-term cardiac memory. **A:** Epicardial action potentials from a control dog (control) and from a dog paced from the posterior left ventricular epicardium for 20 days to induce cardiac memory (memory). The action potentials were recorded from the left ventricular epicardium approximately 1 cm away from the mitral ring. In the setting of memory, the action potential duration is prolonged, and the notch and the plateau of the action potential are more positive. Basic cycle length \(\text{(CL)}\) = 650 ms. (Adapted from Yu et al.\(^12\)) **B:** Action potential duration to 50% \(\text{(APD}_{50}\text{)}\) and 90% \(\text{(APD}_{90}\text{)}\) repolarization measured from epicardial (Epi) and endocardial (Endo) left ventricular tissue slabs dissected from a control dog and from a dog with cardiac memory. \(\text{APD}_{50}\) and \(\text{APD}_{90}\) were measured during pacing at cycle lengths \(\text{(CL; horizontal axis)}\) ranging from 2,000 to 400 ms. The areas between \(\text{APD}_{50}\) and \(\text{APD}_{90}\) of the epicardial and endocardial preparations are \textit{shaded}. Almost all values for endocardium differ from those at corresponding cycle lengths in epicardium \(\left(P < .05 \text{ for all}\right)\) in the control dog. In the memory dog, this was seen only for \(\text{APD}_{90}\) at the two longest cycle lengths \(\left(P < .05\right)\). (Adapted with permission from Shvilkin et al.\(^3\))
apicobasal changes in repolarization occur along with long-term CM has not yet been investigated.

CM also has been described in canine atrium, via calculation of an atrial gradient from X, Y, and Z loops of PTa waves. Pacing from sites that alter atrial activation (e.g., left atrial appendage) induces an atrial gradient change within 2 hours. Although this tends to increase with increases in pacing rate or duration of pacing, its accumulation is masked by the concomitant occurrence of atrial arrhythmias whose P wave is similar to that of the sinus P wave and that compete with both the sinus and paced rhythms. The net result is a multifocal pattern (sinus rhythm, arrhythmia plus atrial pacing) that obscures the reading of the atrial gradient, and the question of whether or not change has occurred must await termination of atrial pacing. Once there are only two competing foci (sinus rhythm and a single competing arrhythmia), the change in gradient evolves clearly. Not only is the atrial gradient change increased in the setting of an ectopic atrial tachycardia, but this occurs even more so at rapid rates before onset of atrial fibrillation. In the former instance, effective refractory period (ERP) measurements show no change; in the latter, ERP is decreased.

It should be emphasized that the atrial gradient is not easily measured and that studies using variables other than the atrial gradient (atrial ERP or atrial action potentials) have not shown occurrence of memory. Nevertheless, the gradient measurement is consistent when excess competition does not interfere with it, and it incorporates data from more sites than do measurements of ERP or action potential duration. In sum, as opposed to CM in ventricle, which has been clearly identified and agreed upon and to date has been unassociated with overt pathology, memory in atrium remains the subject of controversy, is difficult to measure, and appears associated with an arrhythmogenic substrate. Moreover, if one accepts Rosenbaum’s dictum that CM is unassociated with pathology, the changes seen in atrium arguably might be considered to be those of pathologic remodeling rather than CM.

Most of the research on the mechanisms for action potential changes of long-term CM has been performed on ventricular epicardial myocytes in which the decreased phase 1 notch and altered repolarization result in part from a decreased transient outward potassium current (\(I_{\text{to}}\)) density, as well as more positive activation and delayed recovery from inactivation of \(I_{\text{to}}\). Reductions also are seen in mRNA levels for Kv4.3 and in protein and mRNA levels for KChIP2, the pore-forming unit and an accessory protein for the \(I_{\text{to}}\) channel, respectively.

Changes in other ion currents are associated with the occurrence of CM. The L-type calcium current \(I_{\text{Ca,L}}\), which contributes to the maintenance of the action potential plateau, activates at more positive membrane potentials and remains open for a longer period of time in epicardial myocytes from dogs with long-term CM than in controls. This change in \(I_{\text{Ca,L}}\) can contribute to the heightened and prolonged epicardial action potential plateau associated with CM. In addition, the rapidly activating delayed rectifier potassium current \(I_{\text{Kr}}\) shows a reversal of its transmural gradient (normally epicardial \(I_{\text{Kr}} > \)endocardial). This change is accompanied by an increased endocardial ERG, the pore-forming protein for \(I_{\text{Kr}}\). In contrast, no significant change is seen in the slowly activating component of the delayed rectifier \(I_{\text{Kr}}\).

Transmembrane ion currents are only one important determinant of action potential contour. Gap junctions, which facilitate cell-to-cell communication via low-resistance intercellular connections, also contribute significantly. In long-term CM, there is reduced expression of the gap junctional protein connexin43 (Cx43). In addition, Cx43 that normally is localized at the ends of adult ventricular myocytes is redistributed to the lateral margins of the cell membrane when long-term CM is induced. The contribution of this altered Cx43 density and localization to the repolarization changes of CM is under study.

Regulating T-wave changes of CM

We decided to use the regulation of memory in the central nervous system (CNS) as a template for that of CM, as neuronal memory has been a subject of intensive investigation for decades. Figure 3 shows a schema for CM based on transduction pathways initially explored in the CNS. In brief, CM in the ventricle likely is initiated by pacing-induced, altered stress–strain relationships. In cardiac cell cultures, altered stretch induces angiotensin II synthesis and release. Results of intact animal and single myocyte experiments are consistent with a role for angiotensin II in CM induction. For example, angiotensin-converting enzyme (ACE) inhibition, AT-1 recep-
tor blockade, and tissue chymase inhibition prevent occurrence of short-term CM in situ.2 Although studies of single myocytes from normal hearts show that epicardial \( I_{Na} \) is blocked by exposure to angiotensin II, accumulation of long-term CM is unaffected by ACE inhibition or AT-1 receptor blockade (possibly due to up-regulation of the AT-1 receptor, although this remains hypothetical).14 Because angiotensin II increases \( I_{Ca, L} \), we thought that intracellular \( Ca^{2+} \) might transduce short-term and long-term CM.2 We found that nifedipine block of \( I_{Ca, L} \) attenuates short-term and long-term CM accumulation in canine heart.14

With respect to long-term CM, we found that, as in CNS, protein synthesis inhibitors clearly attenuate development of memory.3 Also, at least one \( Ca^{2+} \)-regulated transcription factor, the cAMP response element binding protein (CREB), appears to play a pivotal role in cardiac and in CNS memory accumulation.13 Interestingly, the genes for Kv4.3 and KChIP2 both show CREB binding capability in their promoter regions.13,18 That CREB actually does regulate KChIP2 by direct binding in the promoter region is strongly suggested by a study in which a CREB antisense construct injected into canine left ventricular epicardium induced loss of the phase 1 notch in monophasic action potential recordings and loss of \( I_{to} \).18 Involvement of additional transcription factors in induction of CM is more than likely and awaits investigation.

**Clinical implications of CM**

**Clinical manifestations and differential diagnosis of CM**

CM has been described frequently in patients.2 Its rapid onset in humans is such that episodes of abnormal ventricular activation as short as 1 minute in duration may exert lingering effects on repolarization once normal ventricular activation has resumed.19 The first prospective study investigating long-term CM in humans was reported recently. Wecke et al5 demonstrated that CM assessed vectorcardiographically in man evolves rapidly, is expressed fully within 1 week after the onset of pacing, and dissipates within 4 weeks of cessation of pacing.

As mentioned earlier, CM can confound the diagnosis of cardiac ischemia. For example, T-wave inversions (TWI) caused by right ventricular pacing are difficult to distinguish electrophysiologically from the diffuse TWI associated with critical proximal left anterior descending artery disease. However, Shvilkin et al20 compiled electrocardiographic criteria to help differentiate between the two: the combination of (1) positive T_{vL}, (2) positive or isoelectric T_{v}, and (3) maximal precordial TWI > TWI_{H} was 92% sensitive and 100% specific for CM, discriminating it from ischemic precordial TWI regardless of the coronary artery involved (Figure 4).20 This observation in no way obviates the need for other measurements, such as serum concentrations of specific enzymes, for differentiating ischemia from CM.

**Cardiac memory, arrhythmogenesis, and antiarrhythmic drug therapy**

Although CM itself does not require therapy, it may influence a substrate’s potential to be arrhythmogenic and may modulate the effects of antiarrhythmic drugs. As described in experimental models (resembling CM models) and in human trials, the activation patterns initiated by epicardial pacing may increase transmural dispersion of repolarization and prolongation of the QT interval.21–23 That this may increase the propensity for arrhythmias such as torsades de pointes is illustrated by a case in which a patient repeatedly developed torsades de pointes shortly after initiating epicardial pacing but developed no such arrhythmia during endocardial pacing.23 Moreover, several studies have shown synergy between QT prolongation due to epicardial pacing and \( I_{Kr} \)-blocking antiarrhythmic drugs. For example, Haverkamp et al24 reported increased QT prolongation due to sotalol in a patient in whom CM was observed after ablation of AV reentrant tachycardia. The patient previously had tolerated the administration of sotalol well, without excessive QT interval prolongation.

A study of antiarrhythmic drug effects in short-term and chronic canine cardiac memory models showed the magnitude of the repolarization-prolonging effect of individual drugs may be augmented or diminished as memory evolves, leading to potential proarrhythmia or decreased efficacy, respectively. These differences in drug actions were explained in part by the ion channel-blocking characteristics of each drug.25 The effects on ion channels of cardiac memory and interactions with antiarrhythmic drugs may help us understand apparent inconsistencies in the expression of drug effects among patients and in any one patient over time.

**CM and pacing-induced cardiac remodeling**

The molecular changes characterizing long-term CM reviewed here occur as consequences of cardiac pacing. In other words, ventricular pacing, long thought to be a “neutral” intervention with regard to cellular and subcellular function, in fact is a potent modulator of cellular processes. The extent and via what mechanisms these changes impact cardiac function are not yet completely clear. However, data suggest that pacing-induced changes associated with CM are regionally dispersed according to an altered pattern of contraction and relaxation determined by the location of the pacing electrode.13 These observations regarding CM may help us understand the altered heterogeneity of repolarization and/or calcium handling induced by pacing in a variety of circumstances. For example, a number of publications have stressed the location of ventricular pacing site to altered stress–strain and contractile patterns in the myocar-
Moreover, it has become clear that although ventricular pacing is lifesaving in the setting of complete heart block, the site of pacing may, in the long run, predispose to congestive heart failure. Hence, whether pacing is performed to normalize ventricular rhythm or to treat patients with congestive failure, the long-term goal of optimizing ventricular function must be a core determinant of pacing site selection.

A study by Nahlawi et al provides an intriguing observation relating altered contractile function to a previous interval of pacing. Here, right ventricular pacing induced a reduction in ejection fraction that persisted after pacing was stopped. The persistence of the change in ejection fraction after resumption of normal activation argues against the altered activation pathway being the sole cause of ejection fraction reduction. Although not fitting the definition of CM as an electrical phenomenon, this reduction in cardiac function could very well represent a mechanical accompaniment of the same processes as CM.

Given that pacing so markedly influences protein expression of the contractile apparatus and the electrical system of the heart and that there is regional dispersion of these effects, it is clear that the site of pacing is extremely important in determining the actions of pacing on contractility and the susceptibility to arrhythmias. Therefore, the continued study of cardiac protein expression in the setting of pacing is essential if we are to uncover the range of potentials of pacing therapies.

**Conclusion**

We are still learning how we can use our knowledge of CM to the benefit of patients. It does appear that by understanding CM and the effects of pacing on the heart, we should improve our comprehension of (1) the meaning of changing T-wave morphologies on ECG, (2) administration of anti-
arrhythmic drug therapy, and (3) application of pacemaker therapy to arrhythmias and heart failure.

We are only beginning to appreciate the effects of pacing on the molecular structure of the heart. However, it is already clear that attempts at optimizing pacemaker therapy for patients will be enhanced by knowledge of pacing effects on transcriptional proteins, ion channels, calcium handling proteins, and other structural proteins. That knowledge, combined with a thorough understanding of the substrate characterizing individual patients, may provide a powerful means for determining ideal lead locations and paradigms for cardiac pacing.

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References

