CELL TO BEDSIDE

Cardiac memory: A work in progress

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Cardiac memory is a form of electrophysiological remodeling generally considered benign, although it shares transduction pathways with factors that may be pathological, such as angiotensin II and reactive oxygen species. When induced by electrical pacing, memory provides a window into the mechanisms engaged during cardiac device therapy. Emphasis is placed on the complexity of signaling processes occurring downstream to the simple intervention of cardiac pacing and the relationship of resultant ion channel changes to their expression in action potentials and body surface recordings.

KEYWORDS Cardiac pacing; T waves; Electrocardiography; Vectorcardiography; Repolarization gradients; Ion channels; Connexins; Gene transcription

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Introduction

Nearly 30 years have passed since the late Mauricio Rosenbaum and colleagues[1] provided a name for a T-wave change that was neither primary (i.e., activation-dependent and following the vector of the QRS complex that preceded it) nor secondary (i.e., completely independent of the QRS complex and intrinsic to repolarization alone). It had previously been reported in association with intermittent left bundle branch block, ventricular extrasystoles, right ventricular pacing, posttachycardia syndrome, and ventricular preexcitation.[2] Common to all interventions were abnormal ventricular activation resulting in a T wave during subsequent sinus rhythm that maintained the vector determined by the earlier, abnormal QRS complex. This characteristic was used to define the phenomenon. Rosenbaum et al[1] said the T wave "remembered" the abnormal QRS vector; hence the name cardiac memory. Rosenbaum et al[1] opined that altered electrotonus might underlie memory, an idea supported by the experiments of Costard-Jackle et al[3] using monophasic electrode recordings in Langendorff-perfused rabbit hearts. The matter of mechanism then rested until the late 1980s, when one of us (M.R.R.) was prevailed upon by Mauricio to dig a little further into the causality of memory before he began losing his own. Work in our and other laboratories[3–14] has since provided a diversity of information: the simple T-wave change persisting after abnormal activation has multiple causes, all of which seem convergent on altered myocardial stretch. Downstream linkage is via several signal transduction systems and ion channels (including the gap junctional channels responsible for cell–cell coupling and electrotonus). The transduction systems and channels involved share roles in some instances of cardiomyopathy, myocardial ischemia, and congestive failure, but the mechanisms in memory are engaged by a simple experimental intervention: pacing from a ventricular point source to alter activation (see Figure 1 for template). To summarize, although there are multiple forms of cardiac remodeling, cardiac memory can be thought of as a tightly defined (electrocardiographically) form of remodeling with a causality that has some factors in common and others distinct from other forms of remodeling.[1,2,8,11,14]

Looking for memory, the long and the short of it

Rosenbaum et al[1] showed that as the duration of pacing is prolonged, so is the duration of memory (although the latter persists longer than the inciting event). Based on this information and preliminary experiments, we arbitrarily designated pacing periods of 15 minutes to 2 hours as resulting in short-term memory (lasting minutes to hours), and pacing periods of 2 to 3 weeks as resulting in long-term memory (persisting weeks to months).[8,11,14] Subsequent experiments have shown these categories to be mechanistically distinct because short-term and long-term memory differ in causality while manifesting the same T wave changes (although of generally larger magnitude in long-term memory). Both short-term and long-term memory share the characteristics, described by Rosenbaum, of accumulation (a function of both the abnormal activation and the repetition of abnormal activation, e.g., by increasing pacing rate) and of resolution, such that they are reversible over minutes to hours for short-term memory and weeks to months for long-term memory.

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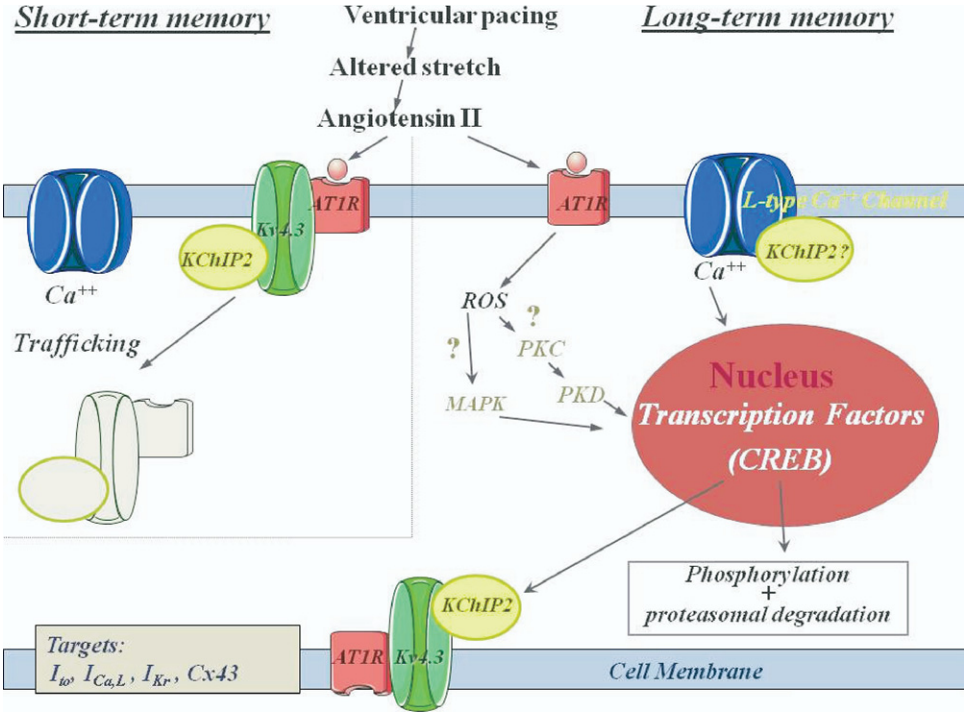

Figure 1 Schematic of pathways already identified and under study in short-term and long-term cardiac memory. Initiation in all cases is via an intervention (here, ventricular pacing) that alters stretch resulting in increased cardiac angiotensin II synthesis/release. Short-term memory results from angiotensin II-induced trafficking of an AT1 receptor/Kv4.3/KChIP2 macromolecular complex. The result is reduction of I_{to}. Long-term memory is initiated by angiotensin II binding to its receptor leading to reduction of the transcription factor CREB. Production of reactive oxygen species (ROS) leading to MAPkinase- and protein kinase C/D-determined pathways are under investigation as intermediary steps. CREB is phosphorylated and then proteasomally degraded, resulting in reduced KChIP2 transcription and expression and decreased I_{to}. Other ion currents altered in memory include $I_{Ca,L}$ and I_{Kr}. Connexin43 is also involved. Ca^{2+} is an important cofactor throughout.

In beginning to query the mechanisms responsible for memory, we searched the literature for a frame of reference. Particularly instructive were the experiments of Kandel et al[15] on long-term potentiation (LTP) in the sea slug, *aplysia californicus*. Memory in *aplysia* could be elicited using a stimulus (electrical shock) that led to withdrawal of its feeding siphon. The slug could be trained such that longer/more repetitive shock periods resulted in longer siphon withdrawal, the duration of which provided a measurement of memory. The transcription factor was the cyclic AMP response element binding protein, CREB.[15]

LTP became the template: we could pace the heart to induce memory of various durations and study its transduction, its transcription, and its expression in downstream proteins in the form of altered ion channels and gap junctions that might impact functionally on repolarization.

Pacing, activation, stretch, and memory

Prinzen et al[4,5] used magnetic resonance imaging to show that ventricular pacing alters the pattern of contraction and relaxation throughout the canine left ventricular (LV) wall. This research led us and others to ask whether altered activation or resultant altered stress–strain relationships are requisite for inducing cardiac memory. Jeyaraj et al[6] studied wedge preparations from hearts of dogs that had undergone 4 weeks of LV pacing to induce long-term memory. They described increased circumferential strain in late-activated segments of myocardium and selective prolongation of action potential duration (APD) in late-activated compared with early-activated myocardial segments. This led them to propose that amplified repolarization gradients between LV segments are the basis for the T-wave changes of cardiac memory. This result expanded on the finding of Shvilkin et al[14] that APD at single sites in epicardial and endocardial LV slabs was prolonged in long-term memory, although this study considered only transmural gradients. These studies also showed that memory is not associated with altered coronary flow, ischemia, or structural remodeling.[6,14]

Sosunov et al[16] showed that altered ventricular stretch but not altered ventricular activation initiates memory in isolated perfused rabbit hearts. They prevented ventricular pacing-induced cardiac memory by decreasing ventricular load or contractility and could induce memory by locally applying stretch to the LV epicardium during normal activation. These findings are consistent with a preliminary in vivo finding that altering canine LV anterior wall stretch during normal activation results in a T-wave vector change comparable to that induced by ventricular pacing.[17]

Assuming that altered stretch is important to initiation of cardiac memory, what is the mediator linking it to the T-wave vector change? Sadoshima et al[18,19] showed that altered stretch causes rapid synthesis/release of angiotensin II in myocyte–fibroblast cultures and that angiotensin II engages stretch-initiated signal transduction pathways. Ricard et al[8] then showed that angiotensin II receptor blockade, angiotensin-converting enzyme inhibition, or tissue protease inhibition reduces the accumulation of short-term cardiac memory (e.g. Figure 2A). The tissue protease result suggests the angiotensin II is locally synthesized rather than circulating.

Calcium is an important cofactor in memory initiation. In intact animals, nifedipine infusion prevents induction of short-term memory and chronic administration of amlodipine reduces the magnitude of long-term memory.[9] The influence of Ca^{2+} here might be via 2 mechanisms: as an upstream factor in signaling cascades important to memory and/or by influencing repolarization gradients through Ca^{2+} channels.

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