Why T waves change: A reminiscence and essay

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The following article is a personal reflection on my study of a subject which has long interested me. The subject is the T wave, and especially the T wave changes occurring as a marker of cardiac memory. My interest evolved over coffees that Mauricio Rosenbaum and I used to share at the Hotel Algonquin during his frequent trips from Buenos Aires to New York. There is something about the Algonquin, whose scarred wooden tabletops carry the imprints of Robert Benchley, Dorothy Parker, and the 1920's New York literati, and there was something about Mauricio—clinician-scientist, friend, and raconteur extraordinaire—that made his repeated challenges to me to "look at cardiac memory before you begin losing your own" irresistible. So began my personal voyage into trying to understand the T wave. My guideposts were the experiments of Wilson and Finch,[1] the astute observations of a host of investigators who followed, and Mauricio's iconoclastic insights. The story is far from over . . . I doubt I'll see the end of it in my lifetime. But if the beauty of discovery is in the voyage, then it has been – for me - a memorable trip.

KEYWORDS Cardiac memory; Ventricular pacing; Ion channel trafficking; Ion channel gene transcription; Transient outward potassium current

ABBREVIATIONS 4-AP = 4-aminopyridine; **AP-1** = activator protein-1; **CREB** = cyclic adenosine monophosphate response element binding protein

(Heart Rhythm 2009;6:S56–S61)

In 1923, Wilson and Finch[1] performed a simple experiment in which ice water was ingested and an ECG was recorded. The result led them to describe T-wave changes as either primary, arising "from disturbances in the function of fairly large regions of ventricular muscle," or "secondary to changes in the form of the QRS complex" and persisting as long as the QRS changes were present. Knowledge of primary T-wave changes has expanded over the years to incorporate those induced by structural alterations, such as hypertrophy, as well as pharmacologic and electrolytic influences and, more recently, channelopathies. Examples of secondary T-wave changes include those induced by conduction abnormalities, ventricular arrhythmias, and myocardial infarction.

However, every story has caveats. One for the categorization of T-wave changes as primary or secondary was noted by several groups of individuals and formalized by Mauricio Rosenbaum[2] (Figure 1). The caveat was a change in the T wave that appeared at first to be secondary (as it was initiated by a change in the QRS complex) but persisted long after the QRS had normalized, such that it mimicked a primary change. Rosenbaum and associates[2] referred to such T waves as "pseudoprimary" and—given the property of the persistent T wave to follow the vector of the inciting QRS complex called the phenomenon "cardiac memory" (Figure 2 [1b]). They performed animal and human experiments on cardiac memory and concluded—although not definitively—that altered electrotonic coupling among cells might provide the mechanism. Studies of Langendorff-perfused rabbit hearts in Michael Franz's laboratory gave further credence to this idea.[3]

Because we recently summarized our own experiments and those of other groups that bear on repolarization and cardiac memory,[4] my goal in this article is to provide a more personal description of the events that have occurred since my coffees with Mauricio. The process has been one of growth and education. I started as a cardiologist who viewed electrophysiology as a be-all and end-all. Electricity was sacrosanct . . . it was the property of cables and batteries, and I tried to simplify everything I saw biologically to fit that context. However, exploring the machinations of the T wave has led to collaborations with colleagues in molecular biophysics, molecular biology, and signal transduction, and together we have explored the mechanisms determining the electrical output (the T wave) of an electrical signal generator (an electronic cardiac pacemaker). Although this has been a personal voyage, it has not been a solitary one. The research throughout has been performed in partnership with Peter Danilo and Ira Cohen, and along the way there have been significant contributions by Susan Steinberg, Rich Robinson, and Penny Boyden.

Our adventure, coupled with parallel discoveries by colleagues in other laboratories with interests in remodeling and in channelopathies, has led me to marvel at the complexity of events leading to seemingly simple changes in

This work was supported by USPHS-NHLBI Grant HL-67101. Dr. Rosen has no conflict of interest. **Address reprint requests and correspondence:** Dr. Michael R. Rosen, Columbia University, 630 West 168 Street, PH7West-321, New York, New York 10032. E-mail address: mrr1@columbia.edu.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2009.07.022

Figure 1 Mauricio Rosenbaum (1921–2002). (Photograph courtesy Charlie Antzelevitch.)

electrical output while I despair of ever learning all the answers. In any event, in querying "why T waves change," I offer the following summary of what we have learned and how we learned it. Figure 2 provides an annotated roadmap of the experimental results.

Starting off . . . the T-wave change

Ughetta del Balzo and I began with a variant on the Rosenbaum model of memory, pacing dogs from the ventricle for 20 to 30 minutes at about 5% faster than their sinus rate, and interspersing this with sinus rhythm or atrial pacing (Figure 2 [1a and 1b]).[5] Following the Rosenbaum lead, we referred to this as short-term memory, and based on the literature we hypothesized that the T-wave change resulted from an altered T-wave gradient consequent to altered transmural dispersion of I_{to} (Figure 2 [6]). To test a potential role for I_{to} in short-term memory, we infused dogs with 4-aminopyridine (4-AP), to nonselectively block I_{to}. In the presence of 4-AP, memory could not be induced. Subsequently, Christoph Geller created a memory model in isolated, paced ventricular epicardial and endocardial slabs. Here, the "T wave" change (the result of processing the epicardial and endocardial action potentials through a difference amplifier) was prevented by 4-AP.[6]

Why did ventricular pacing elicit these changes? Was it the electrical shocks . . . the altered activation . . . the resultant alterations in myocardial stretch (Figure 2 [2])? Sadoshima and Izumo[7,8] previously showed that altering stretch in myocyte–fibroblast cultures results in angiotensin II synthesis and release. Philippe Ricard[9] hypothesized that if altered myocardial activation *in situ* resulted in altered stretch and angiotensin II availability, then interfering with angiotensin II synthesis or binding to its receptor should prevent memory from evolving (Figure 2 [3]). He was right. He could not produce short-term memory in the presence of an angiotensin-converting enzyme inhibitor, an AT-1 receptor blocker, or a tissue chymase inhibitor. That a tissue chymase inhibitor prevented memory induction was consistent with angiotensin II being synthesized in the heart rather than carried from other sites via the circulation. The same experimental series also demonstrated that nifedipine attenuates the evolution of short-term memory, consistent with a role for Ca^{2+} in the process (Figure 2 [5a]).

The next step was to develop a model for long-term memory. Joris de Groot and I performed a series of mapping experiments to document the magnitude and consistency of T-wave changes induced by test pacing at multiple epicardial sites. This provided Alexei Shvilkin with a template for ventricular pacing of chronic dogs that incorporated ease of lead implantation and a T-wave change of sufficient magnitude for consistent study. Shvilkin et al[10] then demonstrated that about 3 weeks of pacing could induce long-term memory that persisted for weeks in the absence of coronary flow changes, failure, or hypertrophy, and that evolution of long-term memory was delayed but not prevented by AT-1 receptor blockade or calcium channel blockade (Figure 2 [5b]).[10] As part of these experiments on long-term memory, we studied left ventricular epicardial and endocardial transmembrane action potentials and found an altered transmural gradient, with epicardial potentials lengthening more than endocardial, while the action potential notch diminished.[10]

How did these changes at the cellular level play out in the heart *in situ?* Giel Janse, Ruben Coronel, and Tobias Opthof joined us to study the T-wave changes in short-term memory (Figure 2 [7a]). The experimental plan included long days of mapping and long nights at Peter Luger's Steakhouse. Under control conditions (during the days), we found a left ventricular apicobasal gradient with the shortest repolarization times anterobasally and the longest repolarization times posteroapically. There was no significant transmural gradient in atrial-paced controls or after 2 hours of ventricular pacing.[11] Because both repolarization time and monophasic action potential durations shortened during induction of short-term memory, we proposed that the deep T wave of short-term memory might be explained by the steeper phase 3 of repolarization. We then studied long-term memory (Figure 2 [7b]) and found no transmural gradient in the control setting.[12] However, a gradient appeared during long-term memory, with epicardial repolarization being longer than endocardial.

This contrasts with the finding of David Rosenbaum's laboratory[13] that long-term memory is associated with disproportionate and localized action potential prolongation of late-activated myocardial segments, but without changes in transmural action potential duration gradients. However, their study design was different because it centered on isolated wedge preparations from dogs in long-term memory. Using yet another study, design, and species, Yoram Rudy's group[14] used ECG imaging to study patients undergoing radiofre-