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Editorial Comment

The U Wave and the M Cell*

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Historical background. The quest for the origin of the U wave, like that for the source of the Nile, has been long and frustrating. The original postulate of Einthoven (1), who identified and labeled the U wave in the early years of this century, was that the U wave represents currents generated by a late repolarizing region of ventricular myocardium. However, despite several false sightings, including the ventricular septum and the papillary muscles (2,3), the identification of a region of myocardium with distinctly prolonged repolarization compared with the remainder of the ventricular myocardium, prolonged enough to account for the U wave, escaped detection until very recently. Mapping of refractory periods throughout the heart, recording of local T waves and recording of intracellular potentials disclosed heterogeneity of durations of repolarization throughout the myocardium with a distribution that explained the general vectors of the T wave (4) but not the U wave.

The large diameter and poor contractility of the fibers in the subendocardial Purkinje network made these fibers the principal objects of study in the beginning of the microelectrode era of cardiac electrophysiology. It was observed (5,6) that Purkinje cells in the free strands, the "false tendons," generated action potentials with a repolarization considerably longer than that of the ordinary myocardial cells. This observation led Hoffman and Cranefield (7) to propose, as a variant of the Einthoven hypothesis, the subendocardial Purkinje network as the source of the U wave. This hypothesis was supported indirectly by observations by Watanabe (8) and others. However, skeptics were concerned that the repolarizing current produced by the small mass of the Purkinje system would be too faint to produce the U wave at the body surface, especially in light of the finding that only discrete sites in the free strands had a very prolonged repolarization, whereas in much of the subendocardial network, the duration of repolarization was only modestly longer than that of myocardium (9).

A competing and mechanistically different hypothesis was offered after the discovery that afterdepolarizations, initially described in neural tissue (10), could be generated by myocardial cells under certain conditions in vitro (11). Nahum and Hoff (12) suggested that afterdepolarizations might be generated by normal myocardium in vivo and be responsible, not only for the U wave, but also for premature beats, commonplace phenomena in normal as well as abnormal hearts and, like the U wave, unexplained. This hypothesis, relentlessly championed by Lepeschkin (13) was abandoned with the advent of intracellular recording because, in general, normal cardiac cells did not generate afterdepolarizations. The hypothesis received a boost recently when it was observed that normal myocardial cells can generate delayed afterdepolarizations with adrenergic stimulation (4). A related concept, that of electrical potentials related to mechanical events (i.e., stretching of fibers in early diastole) has had a contemporary revival (14,15).

M cells. The discovery of M cells by Sicouri and Antzelevitch (16) has again kindled interest in the venerable Einthoven hypothesis. The properties of M cells in the dog fulfill fundamental requirements: 1) The action potentials of M cells are distinctly longer than those of other myocardial cells; 2) the duration of repolarization is long enough, at least at slow rates, to match the timing of the U wave in the cardiac cycle; 3) the mass of M cells appears to be substantial, occupying up to 40% of the left ventricular wall in dogs (17). M cells have other characteristics that fit the features of the U wave. The durations of the action potentials of M cells prolong disproportionately at slow rates in concordance with the long observed prominence of U waves at slower rates. The M cells are prone to develop afterdepolarizations, especially early afterdepolarizations, a property that fits the old observation that premature ventricular beats are most prevalent during the period coinciding with the U waves (13).

The report by Drouin et al. (18) in this issue of the Journal, demonstrating M cells in ventricular slices from explanted hearts, is a quantum leap toward acceptance of the Einthoven M cell hypothesis. The basic properties of the human M cells correspond to those of their more extensively characterized canine counterparts. A plausible temporal correspondence of repolarization of M cells and the U wave at slow rates was demonstrated. Their lovely illustration, albeit contrived, of the concordant rate dependence of M cell repolarization and U waves, with a premature atrial beat during sinus bradycardia, is especially compelling. The human M cells, like those of the dog, occupy a substantial volume of the ventricular wall (estimated at 30%) so that it is credible that their repolarizing currents could generate a discernable deflection on the electrocardiogram (ECG).

Discordant observations. Certain dissonances remain. The differences in repolarization of M cells and other myocardial cells are pronounced only at unphysiologically slow rates. To illustrate the apparent coincidence of the U wave in vivo and the repolarization of M cells in a preparation ex vivo, Drouin et al. selected an ECG from a patient with pathologic sinus bradycardia and a heart rate of 30 beats/min. At physiologic rates, the differences in action potential durations are modest and ostensibly insufficient to account for the separation of the

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U wave from the T wave and for its timing. The mean duration of repolarization of the human M cells was 439 ms at a rate of 60 beats/min, only slightly longer than the normal QT interval and only ~90 ms longer than the duration of repolarization of subendocardial myocardial cells. Studies in dog ventricles indicate that the M cell layers are widespread in the free walls and septum. If there is free electrical communication between these layers and adjacent regions (i.e., junctional resistance is low), a relatively gradual transition of the duration of repolarization across the ventricular wall would be expected. Such a distribution of repolarization should produce a prolonged T wave rather than a separate and distinct U wave. A separate U wave implies a relative electrical isolation of the late repolarizing region of myocardium (19). Drouin et al. (18) describe a sharp transition of action potential duration at the epicardial aspect of the M cell layer, suggesting poor electrical coupling, but a "much more gradual" transition in the endocardial direction. However, they concede that these observations are sparse.

Functions of M cells. The physiologic relevance of the M cells is not entirely clear. What functions could this thick layer of myocardium situated relatively close to the epicardium and widespread through the ventricles and septum serve with its properties of prolonged repolarization and presumably contraction, especially at very slow rates? Antzelevitch and Sicouri (17) have suggested that these cells could play a pathophysiologic roles in arrhythmia generation (17). Their prolonged action potentials render them prone to the generation of afterdepolarizations, both early and delayed, and to triggered firing. It is suggested that the triggering of ventricular tachycardias, torsade de pointes, in the long QT syndromes may begin in these layers. Also, their disproportionately prolonged action potentials increase heterogeneity of repolarization and would be expected to promote reentry. Their role in the generation of arrhythmias is speculative, but it is certain that these newly identified myocardial cells with their distinctive properties have generated interest and will generate research in the future.

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