Electrical Heterogeneity, Cardiac Arrhythmias, and the Sodium Channel

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It was not long ago that we thought of the ventricles of the heart as being composed of 2 basic cell types: specialized conducting cells that make up the His-Purkinje system and ventricular myocytes. Studies conducted over the last decade have highlighted the diversity among the cells that comprise the ventricular myocardium, pointing to regional differences in the electrical properties of cells as well as major distinctions in the response to pharmacological agents and pathophysiological states.\(^1,2\) Several interesting differences have been described between endocardium and epicardium, and a unique population of cells located in the midmyocardial layers has been identified and shown to display electrophysiological and pharmacological profiles different from those of epicardium and endocardium. These cells, known as M cells, have been observed in canine, guinea pig, rabbit, pig, and human ventricles.\(^3-8\)

Epicardial, endocardial, and M cells differ in several ways, but principally with respect to repolarization characteristics. Ventricular epicardial and M cells display action potentials with a prominent transient outward current (\(I_{\text{to}}\))-mediated phase 1, giving rise to a notched appearance of the action potential. The absence of a prominent notch in endocardium is a consequence of a much smaller \(I_{\text{to}}\). Similar regional differences in \(I_{\text{to}}\) are found in canine, feline, rabbit, rat, and human ventricular myocytes.\(^1\) Recent studies also indicate that \(I_{\text{to}}\) and the action potential notch are much larger in right versus left ventricular epicardial\(^9\) and M\(^10\) cells. The transmural gradient in the amplitude of the \(I_{\text{to}}\)-mediated action potential notch underlies the normal J wave or J point elevation in the ECG,\(^11\) and its accentuation, particularly in the right ventricle, contributes to the development of life-threatening arrhythmias in patients with the Brugada syndrome and various forms of idiopathic ventricular fibrillation.\(^12,13\)

M cells are distinguished by the ability of their action potential to prolong more than that of epicardium or endocardium in response to a slowing of rate or in response to agents with antiarrhythmic class III actions.\(^2\) These features of the M cell are attributable, at least in part, to the presence of a smaller slowly activating delayed rectifier current (\(I_{\text{Ks}}\)),\(^14\) a larger late sodium current (late \(I_{\text{Na}}\)),\(^1,15\) and a larger sodium-calcium exchange current.\(^16\) No transmural differences are apparent with respect to the rapidly activating delayed rectifier (\(I_{\text{Kr}}\)) and inward rectifier currents in the canine heart. However, transmural and apico-basal differences in the density of \(I_{\text{Kr}}\) channels have been described in the ferret heart.\(^17\)

Electrophysiologically and pharmacologically, M cells display characteristics intermediate between those of Purkinje and ventricular cells. Studies involving canine arterially perfused wedge preparations have shown that transmural voltage gradients generated by differences in the time courses of repolarization of the 3 ventricular myocardial cell types are in large part responsible for the inscription of the electrocardiographic T wave and that amplification of these transmural heterogeneities of final repolarization can lead to the development of the long-QT syndrome.\(^18-20\)

Perfused wedge and in vivo studies have shown that \(I_{\text{Kr}}\) blockers (eg, \(\beta\)-sotalol), calcium channel agonists (eg, BayK 8644), and agents that augment late \(I_{\text{Na}}\) (eg, ATX-II or anthopleurin-A) prolong the QT interval, increase transmural and interventricular dispersion of repolarization, and induce extrasystoles capable of precipitating torsade de pointes.\(^18-25\) Agents capable of prolonging action potential duration (APD), with the exception of the \(I_{\text{Kr}}\) blockers, amplify transmural dispersion by prolonging APD of the M cell more than that of epicardial or endocardial cells and by inducing early afterdepolarizations preferentially in M cells. Similar phenomena are observed in response to \(I_{\text{Kr}}\) blockers, but only in the presence of a \(\beta\)-adrenergic agonist; otherwise, these agents produce a homogeneous prolongation of APD and no early afterdepolarizations.\(^21,26\)

In a recent issue of Circulation Research, Sakmann et al\(^27\) made another important contribution to the heterogeneity literature demonstrating differences in late \(I_{\text{Na}}\) among cells spanning the ventricular wall of the guinea pig heart. Midmyocardial cells are shown to display a smaller late \(I_{\text{Na}}\) than epicardial or endocardial cells. This finding is opposite to that reported for the canine heart, where late \(I_{\text{Na}}\) density is considerably larger in M cells than in epicardial or endocardial cells and contributes importantly to the longer APD of the M cell. The disparity may be attributable to methodological considerations. Experiments involving isolated tissues indicate that the guinea pig heart is similar to that of the dog, containing M and transitional cells in the midmyocardium (deep subepicardium to deep subendocardium) and cells with much briefer APD, showing little response to \(I_{\text{Kr}}\) in the endocardial and epicardial layers.\(^2\) However, unlike the dog, dissociation of myocytes from smaller hearts is fraught with problems, because epicardial and endocardial cells are underrepresented.\(^1,2\) Indeed, studies involving dissociation of myocytes from guinea pig hearts have reported cells with electrophysiological and pharmacological profiles of M and
transitional cells but not of endocardial or epicardial cells.28 Rather than lacking M cells, as suggested, these studies seem to be lacking in epicardial and endocardial cells.1,2 In most regions of the canine heart, M cells displaying the longest APD are localized in the deep subendocardial layers. If the same is true in the guinea pig heart, M cells with the longest APD would be expected to be found in the endocardial fraction. Indeed, previous studies by Bryant et al28 report that guinea pig cells with the longest APD are found in the endocardial fraction. Moreover, a subsequent report by the same groups indicates that these same cells abbreviate most in response to 100 nmol/L tetrodotoxin.29 Both observations are consistent with the finding by Sakmann et al27 of a large late I\textsubscript{Kr} in cells isolated from guinea pig endocardium. Late I\textsubscript{Kr} in ventricular cells has received relatively little attention. Recent studies suggest that it plays a prominent role in maintaining the plateau of the action potential, determining APD and transmural dispersion of repolarization, and development of cardiac arrhythmias, particularly under conditions in which I\textsubscript{Kr} and I\textsubscript{Ks} are reduced (eg, long-QT syndrome, hypertrophic cardiomyopathy, chronic infarction, and heart failure).30,31 Although block of fast I\textsubscript{Kr} has fallen into disrepute as a target for the treatment of ventricular arrhythmias, late I\textsubscript{Kr} should not be dismissed categorically and seems deserving of some attention.

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References
10. Volders PG, Sipido KR, Carmeliet E, Spanjens RL, Wellens HJ, Vos MA. Repolarizing K\textsuperscript{+} currents I\textsubscript{To1} and I\textsubscript{Ks} are larger in right than left canine ventricular midmyocardium. Circulation. 1999;99:206–210.
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