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Letter to the Editor

Are M cells present in the ventricular myocardium of the pig? A question of maturity

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A number of studies have described the presence of M cells in the midmyocardial layers of ventricular myocardium of several species (Table 1) [1-14]. The M cell is distinguished by the ability of its action potential to prolong disproportionately to other myocardial ventricular cells in response to a slowing of rate and/or to agents that prolong action potential duration. The ionic basis for these features of the M cell include the presence a smaller slowly activating delayed rectifier current (I_{Ks}) [1] as well as a larger late sodium current (late I_{Na}) [15]. The unique repolarization characteristics of the M cells have yielded some interesting observations relative to our understanding of the electrophysiology, pharmacology and pathophysiology of the ventricles of the heart as well as some new insights into the basis for the electrocardiographic J, T and U waves [16].

Rodriquez-Sinovas et al. [5] recently confirmed the presence of M cells in the canine heart, but presented evidence for their absence in the porcine heart. Without discounting the value of this fine study, we would like to point out that the work involving the canine tissues was performed using adult dogs, whereas that involving porcine tissues employed pigs 1 to 2 months of age. This difference may be a critically important one in that recent developmental studies indicate that in the dog the M cell is not electrophysiologically distinct until approximately 3 months of age (unpublished observation). The neonatal heart is homogeneous with respect to action potential morphology in the first few days of life. A notched appearance of the action potential gradually appears in epicardial and midmyocardial, but not endocardial, cells in the first few weeks of life due to the accentuation of phase 1, secondary to an increase in the density of the transient outward current (I_{to}) . Differences in the time of repolarization of phase 3 of the action potential among cells spanTable 1

Evidence for the presence of M cells in ventricular myocardium of several mammalian species

Dog	
Myocytes	[1,2]
Tissues slices	[3–5]
Perfused wedge	[6-8]
In vivo	[9,10]
Guinea Pig	
Tissue slices	[11]
Rabbit	
Tissue slices	[12]
Human	
Myocytes	[13]
Tissue slices	[14]

ning the ventricular wall gradually develop over the first few months and are usually not prominent until the third month of life. In the anterior wall of the canine left ventricle, the M cells with the longest action potential appear in the midmyocardial to subendocardial layers [7,8,16]. A similar but small transmural gradient was observed by Rodriquez-Sinovas et al. [5] in the pig, suggesting the presence of M cells in a formative stage of development. A definitive assessment clearly must await studies utilizing older pigs. If the pig indeed is devoid of M cells, it will be the first member of the mammalian species in which this distinction has been demonstrated.

References

- [1] Liu DW, Antzelevitch C. Characteristics of the delayed rectifier current ($I_{\rm Kr}$ and $I_{\rm Ks}$) in canine ventricular epicardial, midmyocardial and endocardial myocytes: A weaker $I_{\rm Ks}$ contributes to the longer action potential of the M cell. Circ Res 1995;76:351–365.
- [2] Liu DW, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocar-

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dial myocytes from the free wall of the canine left ventricle. Circ Res 1993;72:671–687.

- [3] Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle: The M cell. Circ Res 1991;68:1729–1741.
- [4] Anyukhovsky EP, Sosunov EA, Rosen MR. Regional differences in electrophysiologic properties of epicardium, midmyocardium and endocardium: In vitro and in vivo correlations. Circulation 1996;94:1981–1988.
- [5] Rodriguez-Sinovas A, Cinca J, Tapias A, Armadans L, Tresanchez M, Soler-Soler J. Lack of evidence of M-cells in porcine left ventricular myocardium. Cardiovasc Res 1997;33:307–313.
- [6] Antzelevitch C, Nesterenko VV, Yan GX. The role of M cells in acquired long QT syndrome, U waves and torsade de pointes. J Electrocardiol 1996;28(suppl.):131–138.
- [7] Antzelevitch C, Sun ZQ, Zhang ZQ, Yan GX. Cellular and ionic mechanisms underlying erythromycin-induced long QT and torsade de pointes. J Am Coll Cardiol 1996;28:1836–1848.
- [8] Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 as well as LQT3 models of the long QT syndrome. Circulation 1997, in press.
- [9] Weissenburger J, Nesterenko VV, Antzelevitch C. Intramural monophasic action potentials (MAP) display steeper APD-rate relations and higher sensitivity to Class III agents than epicardial and

endocardial MAPs: Characteristics of the M cell in vivo. Circulation 1995;92:I-300 (Abstract).

- [10] El-Sherif NC, Restivo M. The electrophysiological mechanism of ventricular arrhythmias in the long QT syndrome: Tridimensional mapping of activation and recovery patterns. Circ Res 1996;79:474– 492.
- [11] Sicouri S, Quist M, Antzelevitch C. Evidence for the presence of M cells in the guinea pig ventricle. J Cardiovasc Electrophysiol 1996;7:503–511.
- [12] Weirich J, Bernhardt R, Loewen N, Wenzel W, Antoni H. Regionaland species-dependent effects of K⁺-channel blocking agents on subendocardium and mid-wall slices of human, rabbit, and guinea pig myocardium. Pflugers Arch 1996;431:R 130 (Abstract).
- [13] Li GR, Feng J, Carrier M, Nattel S. Transmural electrophysiologic heterogeneity in the human ventricle. Circulation 1995;92:I-158 (Abstract).
- [14] Drouin E, Charpentier F, Gauthier C, Laurent K, Le Marec H. Electrophysiological characteristics of cells spanning the left ventricular wall of human heart: Evidence for the presence of M cells. J Am Coll Cardiol 1995;26:185–192.
- [15] Eddlestone GT, Zygmunt AC, Antzelevitch C. Larger late sodium current contributes to the longer action potential of the M cell in canine ventricular myocardium. PACE 1996;19:II-569 (Abstract).
- [16] Antzelevitch C. The M cell. Invited Editorial Comment. J Cardiovasc Pharmacol Therapeutics 1997;2:73–76.