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Resolving the M-cell debate: Why and how

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Heart Rhythm has recently published a series of articles reflecting a lively and healthy debate about the functional importance of midmyocardial (M) cells.^{1–4} One group of scientists has challenged the now classic notions about the role of M cells in cardiac electrophysiology,^{1,4} while another group has defended the evidence.^{2,3} The three coauthors of the present paper have been invited to resolve the debate and to “agree with one position or the other, or with neither, or conclude that more information is needed before an opinion can be offered.” Rather than comment on the veracity of the observations described in the position papers by these two esteemed groups^{1,2} or the reservations expressed in their rebuttals,^{3,4} we chose to briefly summarize the main points of contention, to review the significance of the issue, and to describe additional work that could provide new insights into the pertinence of the M-cell concept to *in vivo* physiology.

What is the disagreement?

There are many points of agreement between both sides in the debate. Both agree that M cells are well documented in studies in isolated cells and perfused cardiac wedge preparations, but they disagree as to their functional significance, pointing out discrepant observations.^{1,2} Both agree that cell-to-cell coupling attenuates repolarization differences in the intact heart, a phenomenon that is lost in isolated cells and possibly attenuated in cut-surface wedge preparations. The principal point of disagreement relates to the interpretation of a variety of observations that use activation–recovery intervals as an index of action potential duration in intact hearts and were unable to detect intramural zones of delayed repolarization.¹ The anti-M-cell group claims that these observations invalidate the M-cell concept, whereas the pro-M-cell group argues that this evidence is weakened by a number of deficiencies: (1) the indirect nature of the activation–recovery interval as a repolarization index; (2) the intrinsic electrophysiologic effects of general anesthetics, many of which may mask transmural repolarization differences by blocking the late sodium current (late I_{Na}), whose prominence in M cells forms a large part of what makes these cells distinctive; and (3) the complex distribution of M cells, which could cause them to be missed with the limited number of plunge needles that have been used to record transmural activation–recovery intervals in intact hearts.

Who cares?

It is reasonable to take a step back and ask why anyone should care about the existence of M cells. Is this a theoretical argument akin to the medieval philosophical debates about how many angels can dance on the end of a pin, or does it have practical significance? We would argue that the *in vivo* relevance of the M-cell concept is an important one that needs to be resolved. The concept has been used to explain many biologic phenomena, such as the basis of electrocardiographic J and T waves,^{5,6} the ECG changes and pharmacologic responses characteristic of congenital rhythm disorders,⁷⁻⁹ and early proarrhythmic responses to cardiac resynchronization therapy.¹⁰ The usefulness of the wedge preparation in predicting long QT syndrome (LQTS)/torsades de pointes (TdP) liability is predicated on its physiologic relevance, of which M cells are a substantial component.¹¹ M-cell properties have been used to explain many electrophysiologic phenomena with great importance.¹² If M cells are not functionally important in the intact heart, the mechanisms of a wide range of phenomena would need to be rethought and reexamined.

The applicability of the M-cell concept is also relevant to future therapeutic development. If M cells are important in arrhythmogenesis, it is appropriate to think of ways to target them. For example, it might be desirable to search for repolarization-delaying Class III agents (and related ion channel targets) that have reduced effects on M cells and equalize, rather than exacerbate, transmural dispersion of refractoriness to preclude TdP risk. The role of M cells also justifies a search for compounds to selectively accelerate M-cell repolarization for the management of conditions with LQTS pathophysiology. Finally, it may eventually be possible to develop M-cell ablation methods (catheter based or relying on specific molecular/gene therapy targets) as antiarrhythmic therapies. None of these make much sense if M cells are not functionally important in the intact heart.

How to resolve the issue?

Because the main bone of contention relates to lack of confirmation of M-cell physiology in intact hearts, additional definitive *in vivo* evidence is highly desirable. One limitation to *in vivo* studies is the need for general anesthesia to gain access to the heart. Some general anesthetics, particularly the barbiturates, have strong direct electrophysiologic effects including Na⁺ channel blockade,¹³ which can suppress transmural action potential duration (APD) dispersion by reducing M-cell APD.¹⁴ Further *in vivo* searches for M-cell physiology should be obtained with the use of anesthetic/analgesic agents that either are relatively neutral electrophysiologically (e.g., chloralose,¹³ halothane,¹⁴ ketamine¹⁵) or, better yet, would be expected to exaggerate M-cell physiology by suppressing repolarization reserve (e.g., midazolam, propofol).¹⁵ Because of the relatively poor sensitivity of currently available techniques for detecting repolarization heterogeneities, it would be desirable to probe the functional significance of M cells under conditions in which their characteristics are amplified with the use of agents that reduce repolarization reserve. When performed in this fashion, such studies have delineated a contribution of M cells to transmural dispersion of repolarization and to arrhythmogenesis in the *in vivo* heart.^{14,16}

Wedge studies conducted in both canine and human hearts have shown that M cells with the longest APD are generally localized to the deep subendocardium, sometimes extending to the endocardial surface.^{12,17} A criticism of the available *in vivo* studies is the fact that M-cell populations may also be scattered and discontinuous, making them easy to miss. Recent studies in human cardiac wedge preparations have shown discrete islands of cells with M-cell physiology.¹⁷ More work of this type, along with detailed mapping, cell phenotype characterization, and mathematical models assessing functional significance, might help in resolving the role of M cells in man. Analysis of intramural repolarization in intact hearts

with greater resolution also would be helpful. Optical mapping into deeper myocardial layers would be the ideal way to accomplish this and eventually may be possible.^{18,19} Another approach is high-resolution plunge needle mapping. The only available study that used this method obtained mixed results. Midmyocardial APD under control conditions was not significantly greater than that of other layers, but substantial differences were observed under TdP conditions.¹⁶ Mapping during TdP showed subendocardial origin (expected based on the preferential role of Purkinje fibers²⁰ and possibly deep subendocardial M cells¹² in the genesis of early afterdepolarizations) but maintenance via reentry. Further work of this type would be helpful. Finally, novel indices of repolarization amenable to study in intact hearts could be quite useful. For example, Haugaa et al²¹ studied myocardial contraction indices by echocardiographic strain measurements in controls and LQTS patients and found that subendocardial contraction durations are greater than midmyocardial, significantly enhancing transmural dispersion.

Another potential approach would be the development of prospectively testable hypotheses that require the existence of M-cell physiology for validity. Past studies have observed the behavior of M cells, particularly *in vitro*, and used these observations to explain important physiologic phenomena.^{6–10} The elaboration of untested hypotheses that can be valid only if M cells are functional *in vivo*, and their subsequent prospective testing, would be very helpful.

Mathematical modeling of cardiac electromechanical activity has become an increasingly sophisticated tool and, with the rapid increase in computing power and sophistication, promises to shed light on a wide range of aspects of cardiac function.²² Further analysis of the implications of M-cell physiology with the use of such models has the potential to verify predictions, generate new testable hypotheses, and, in combination with rapidly developing imaging technology, provide new and important insights.

Getting past M cells

One final thought on the M-cell debate is that it may be distracting us from seeing the bigger picture. Perhaps we should be taking a wider perspective, looking more globally at the determinants of regional action potential properties throughout the ventricles. Issues such as the ionic basis of apical-to-basal, transeptal, right-to-left, and other regional repolarization disparities merit more attention. A fundamental question that has barely been addressed, and needs to be, is how cellular ion channel function and expression are regulated. Is the relative function of various ion currents that govern APD determined by intrinsic and immutable properties, or are there feedback systems that govern channel function to regulate APD? Some indication of feedback control of ion channel expression has been obtained,²³ but this area is very much underexplored. If regulatory systems do operate, what are the control signals (mechanical, ionic, neurohumoral)? What are the cellular mechanisms coupling control signals to changes in ion channel function? Are regional APD differences due to different embryologic origins or to local conditions of strain, pressure, coronary perfusion, metabolic demands, etc? Deeper thinking in some of these areas could provide insight not only into the M-cell debate but also into much wider aspects of how repolarization is controlled in health and disease. Greater understanding of these fundamental processes could provide openings for new therapeutic approaches about which we can presently only dream.

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