LETTERS TO THE EDITOR

To the Editor—Resolving the M-cell debate: Mechanics Matters

We strongly agree with the summary by Drs. Nattel, Antzelevitch, and Noble[1] on the discussion of M-cell properties, distribution, and relevance: that a forward-looking approach toward designing studies with better discriminatory potential is key to assessing pathophysiologic roles of activation and repolarization patterns *in vivo.*

We wish to highlight one important aspect that tends to be overlooked, namely, that the heart is a mechanically active and mechano-*sensitive* organ. Stretch affects a vast range of cardiac functional properties, including electrical conduction, excitation, and action potential duration (APD)[2] – all relevant to the M-cell debate. Passive and active mechanical properties show significant spatiotemporal heterogeneity during the heartbeat, which is prerequisite for normal cardiac activity, eloquently called "homogeneity out of heterogeneity" by Katz and Katz.[3] This balance is understood to involve feedback loops with different intrinsic time-scales, linking structure, electrics, and mechanics.[4]

If we consider the *in vivo* and *ex vivo* model systems used to study M-cell (and other) electrophysiologic behavior, it is apparent that we are altering (opening of chest and pericardium, excision of the heart, mechanically restraining tissue for optical mapping) or removing (deleting circumferential strain in wedges, applying chemical uncouplers, using mechanically unloaded cells) one crucial input into this well-balanced electromechanical system. Modifying mechanics changes electrics,[2] and if this is regionally heterogeneous (or if tissue mechanosensitivity is inhomogeneous), then alteration of the mechanical environment can contribute to the generation of regional electrophysiologic patterns that may be absent in the intact subject.

How might we square this circle at a time when methods for assessment of transmural activation and repolarization are largely invasive and affect mechanics (even plunge electrodes will do so, albeit presumably with one of the smallest net effects)? One obvious possibility is to develop optical mapping approaches that do not require interference with mechanics over and beyond preparation-imposed constraints. This is particularly challenging for repolarization, but efforts to improve image tracking–based data correction look promising. Another possibility is to conduct transmural observations on "nearly intact hearts," accessing the transmural plane, for example, by cutting off apical segments and looking at the coronary-perfused heart "from below." This could be combined with epicardial imaging, using long-wavelength dyes as mentioned by Nattel et al.[1] More 'outlandish', but approaching the realms of technical possibility,[5] would be magneto-cardiographic exploration of repolarization patterns. Alternatively, echocardiographic strain measurements may offer useful reference indices of repolarization in conscious patients and animals, which could be used to constrain model-derived predictions of *in vivo* local stress–strain distributions,[6] which subsequently can be applied to single cardiomyocytes.[7] For single cell work it will be important to isolate cells specifically from pre-identified "M-cell islands," whether established using electrophysiologic observation or genetic (and other) markers, if and when available (of note, the 3-dimensional topology of M-cell islands/archipelagos is of interest, too, and could be assessed by progressive shaving of apically imaged hearts). In any case, group comparisons of single cell data should be based on pre-identification of M-area origin in native tissue; otherwise, one may end up with "reverse causality" by declaring cells with long APD (L-cells) to be from midmyocardial loci of interest (M-cells).

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