Cardiac response to weak electrical shocks challenges the functional syncytium paradigm.

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The electrical response of myocardial tissue to periodic field stimuli has attracted significant attention as the basis for low-energy anti-fibrillation pacing (LEAP), potentially more effective than traditional single high-energy shocks. While conventional high-energy shocks restore orderly cardiac contractions by resetting irregular electrical activity of cardiac myocytes, low-energy shocks achieve a similar result by producing multiple, simultaneously firing excitation centers, or "hot spots" (HS), which gradually take control over the entire heart until it beats normally. Until this study, understanding the mechanisms of HS formation was hindered by the lack of adequate experimental methods for localizing HS inside the heart wall. Here, we overcome this limitation by using a novel tomographic 3D fluorescent imaging technique employing a near-infrared voltage-sensitive dye which allows the detection and localization of HS without causing tissue damage and perturbing the electrical response. Using this technique, we measured for the first time the depth distribution of the HS and correlated their formation with the anatomical organization of the myocardial tissue obtained by ultra-deep confocal imaging. Contrary to theory, the peak HS distribution is located deep inside the heart wall and the depth is not significantly affected by field polarity. We did not observe the strong co-localization of HS with major coronary vessels anticipated from theory. Yet, we observed considerable lateral displacement of HS with field polarity reversal. Such a distribution cannot be readily explained within the functional syncytium paradigm (electrical continuity of intracellular space across entire myocardium) which is central to cardiac propagation theories. Computer simulations show, however, that by deemphasizing lateral intracellular coupling and accounting for resistive heterogeneity in the extracellular space, the experimental observations are faithfully reproduced. Our findings challenge current paradigms of cardiac excitation and electrical defibrillation. Extended theories based around enhanced descriptions of cellular scale electrical mechanisms may be necessary. The considerable lateral displacement of HS with field polarity reversal supports the hypothesis of biphasic stimuli in LEAP being advantageous.

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