Response to Selvaraj and Nair

We thank Drs Selvaraj and Nair for the opportunity to discuss the clinical relevance of our recent findings in explanted human hearts and to bridge the gap between clinical and basic electrophysiology research methodologies. Using the basic science methodology of optical mapping, which is not yet available in clinical electrophysiological laboratories, we have recently found that end-stage heart failure results in anatomically heterogeneous repolarization remodeling in humans. In this human study, we have used a measure of intrinsic repolarization properties that is commonly accepted in basic studies, action potential duration (APD), which is the basis for activation–recovery interval (ARI) and a close approximation of the functional refractory period (RF) used in clinical studies. Mapping APD dispersion is methodologically challenging in clinical settings, unlike basic research laboratories.

A repolarization map is simply an algebraic sum of the activation map and the map of APD. APD map has become an important characteristic because it represents intrinsic repolarization properties, which are less dependent on activation sequence and more dependent on local functional state, cell–cell coupling, and gene expression responsible for repolarizing currents. Thus, APD dispersion is a frequently used measure for estimation of repolarization remodeling. We are surprised that the authors of the letter found this approach “an artificial measurement with no physiological significance,” given that it was introduced to cardiac electrophysiology by Thomas Lewis in 1925 and, since that time, has been used by numerous groups.

In our early studies, we have demonstrated that APD base-to-apex gradient governs repolarization and RF pattern in the guinea pig heart, because activation is relatively fast, and therefore the conduction delay is significantly shorter compared to global APD gradient. But, if activation were relatively slow, it may indeed influence the repolarization sequence and dispersion. In our present study, activation sequence during endocardial pacing, which represents normal excitation, was similar in all hearts, with activation time ranging from 45 to 70 ms. Our findings are in agreement with the observation of Taggart et al, who demonstrated the absence of the ARI dispersion in patients measured during routine coronary artery surgery using plunge needle electrodes. To address the question of Drs Selvaraj and Nair, we constructed maps of repolarization (data are not shown because of editorial limitations for Letters). Contrary to their hypothesis, repolarization pattern to a significant degree is determined by APD maps in these hearts during endocardial pacing. In a nonfailing heart with 150-ms intrinsic transmural APD gradient (range from 380 to 530 ms), 50-ms transmural activation slightly delayed epicardial repolarization and thus produced 122-ms transmural repolarization gradient, which was governed by APD distribution pattern. In a failing heart with 35-ms transmural APD gradient (range from 435 to 470 ms), 69-ms heterogeneous transmural activation significantly delayed both midmyocardial and subepicardial repolarization and resulted in 40-ms repolarization gradient (range from 485 to 525 ms), which was still governed by APD pattern.

However, in general, we agree that dispersion of repolarization depends on the activation sequence, which indeed could be distorted in failing hearts by scars, regions of ischemia, remodeling, and fibrosis. In our Limitations section, we have discussed the fact that we selected regions of the left ventricles without these structural abnormalities to focus on intrinsic repolarization remodeling. Moreover, this study provided assessment of repolarization in relatively small samples of tissue, which cannot predict global dispersion of repolarization of the whole heart. Unfortunately, we still do not have a methodology to map repolarization in the entire heart in 3D. But optical mapping is a promising first step in this direction. Our follow-up study focuses on this issue.

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