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Letters to the Editor

Human Ventricular Action Potential Duration Restitution

We read with interest the paper by Narayan et al. (1) that related right ventricular (RV) action potential duration (APD) restitution slopes to the presence of T-wave alternans (TWA) and ventricular tachycardia (VT) inducibility in patients with left ventricular (LV) dysfunction (LV ejection fraction [EF] 28 ± 8%). Standard restitution was measured by plotting APD90 as a function of the preceding diastolic interval (DI) during extrastimulus testing (S1S2). The prevalence of steep restitution slopes (>1) was similar between patients with positive or negative TWA, and mean restitution slopes were no different between those with inducible or noninducible VT.

Both these findings are contrary to a study reported by our group in a similar patient population (LVEF 30 ± 8%) (2). We feel this discrepancy can be accounted for by considering differ-
ences in the interpretation and measurement of the minimum DI which can significantly influence the steepness of the standard restitution slope. We determined activation recovery interval (ARI) restitution using a pacing protocol similar to Narayan et al. (1), but at short S1S2 coupling interval where local activation of S2 occurs before repolarization of the preceding S1 the DI is negative and can only be derived by measuring the ARI of the preceding beats of the S1 drive train (2,3). With this approach, the minimum DI (−22 ± 14 ms) is typically negative (2,3), unlike the minimum negative DIs reported by Narayan et al. (19 ± 13 ms) (1). It is not clear how the authors measured DI at the shorter S1S2 coupling intervals, though it is apparent that APD_{90} of the last drive train beat was not reached before the S2 upstroke (Fig. 1C in Narayan et al. [1]). The presence of a negative DI is consistent with effective refractory period/APD ratios less than unity in humans. Without correcting DI at the shorter S1S2 coupling intervals, negative DIs will be under-recognized, which in turn may overestimate and equalize the steepest restitution slope between patient groups.

It is also important to consider the spatial heterogeneity of restitution slopes, which has been implicated in the pathogenesis of alternans and ventricular arrhythmias in experimental and human studies. Although Narayan et al. (1) did not find differences in restitution slopes between the RV apex and outflow tract, nor between the RV and LV endocardium, we have reported steeper ARI restitution slopes at the RV apex compared with the RV base in a similar patient population with impaired LV function (2). Steeper ARI restitution slopes have also been found in the human RV endocardium versus LV endocardium (3).

We would be interested in the authors’ comments on whether the lack of difference in steepest restitution slopes between patient groups or between recording sites could have been influenced by the method used to measure DI at the shorter S1S2 coupling intervals.

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We appreciate the perceptive comments of Drs. Selvaraj and Chauhan on our recent study (1), in which we report that the maximum slope of ventricular action potential duration (APD) restitution did not separate patients with left ventricular dysfunction with or without inducible arrhythmias and did not predict T-wave alternans (TWA) or outcome. The authors suggest that the method used to measure diastolic intervals (DI) may explain similarities in APD restitution between groups, at variance with their recent findings (3).

The slope of the APD restitution relationship at any point relates the change in APD to change in DI. Therefore, slope cannot be influenced by whether the shortest DI is negative (1,2) or zero (3), which would simply translate the restitution curve along the DI axis. We actually used the same method as Selvaraj and Chauhan (2), and many patients did have negative minimum DI.

It is thus intriguing why we could not confirm the authors’ finding that ventricular APD restitution is steeper in “high-risk” patients (2). One likely explanation is that minimum DI in their study was significantly shorter in high- than in low-risk patients (by ~14 ms) (2). As a result, the earliest restitution points in low-risk patients commenced at longer DI that, as the authors note, curtailed the steepest portion of restitution (Fig. 2 in Selvaraj and Chauhan [2]). Notably, minimum DI did not differ between groups in our study (1).

This raises the issue of what may alter minimum DI. The authors used activation recovery intervals (ARI) in unipolar electrograms to estimate APD, which, though validated (4), are less accurate at short DI. Even using the modified Wyatt method, ARI is more likely to underestimate than overestimate APD at short DI (see Fig. 4 in reference 4) and therefore overestimate maximum slope and contribute to an inverse relationship with minimum DI (2). The authors also paced from only 1 right ventricle site, which leads to differing actual DIs at some sites owing to conduction delay. Shorter DI in high-risk patients may also reflect greater “triangulation” of action potential phase 3 (5), potentially explaining different effective refractory period to APD ratios between groups (2), although this is not testable using ARIs.

Our results agree with reports that maximum APD restitution slope exceeds 1 in subjects without left ventricular dysfunction (6,7) and does not differ in mild left ventricular dysfunction patients (8). Although Selvaraj and Chauhan note similarities in restitution slope between historical controls and “low-risk” patients, they do not confirm that this group was arrhythmia free on follow-up (2).

Selvaraj and Chauhan also raise the important issue of spatial heterogeneity in APD restitution. Although restitution slope in our study did not differ between sites in patients with dual-site recordings (1), we agree that greater spatial sampling is necessary to explain spatial nonuniformities in TWA (9) and to define the relative importance of repolarization dispersion and restitution slope to arrhythmogenesis.

We thank Selvaraj and Chauhan for their interesting observations on our work. Further studies are needed to improve our understanding of the dynamic mechanisms initiating life-threatening arrhythmias.

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