In vivo dispersion in repolarization and arrhythmias in the human heart

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In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Chauhan and colleagues (5) have measured dispersion in ventricular repolarization time (RT) in patients with cardiomyopathy and an ejection fraction \( \leq 40\% \). Such data are sparse in humans in general. The measurements have been made at the right ventricular (RV) endocardium and at the left ventricular (LV) epicardium by a catheter in the great cardiac vein. This study by Chauhan et al. (5) is one of the very few with data from the endocardium and epicardium in the same patients. Also, the patients were conscious. RT dispersion was in the order of 10–12 ms/mm in 12 patients in which either ventricular tachycardias (VT) could be provoked or in which there was positive microvolt T wave alternans (TWA). In 10 patients without VTs or TWA, RT dispersion was limited to 2–3 ms/mm. A similar increased dispersion in activation-recovery intervals (ARI; an index of local action potential duration), but not dispersion in activation times, was shown to underlie the difference in RT dispersion between the two patient groups.

HISTORICAL ASPECTS

Durrer and colleagues (12) described in 1970 the total activation of the normal human heart in great detail. Had they looked another 350 ms later in their recordings, we would now know the repolarization pattern of the human heart at the same accuracy (9). Our present understanding is that at 1 Hz total repolarization takes <400 ms, yet we do not know the repolarization pattern. Dispersion in repolarization is considered highly arrhythmogenic. The assessment of such dispersion is not without debate (for review, see Ref. 6), and it has been questioned whether local dispersion can be appreciated from the surface ECG at all (4). To date, it seems reasonable to assume that a large QT dispersion in the ECG results from a large dispersion in RT, which is highly arrhythmogenic. However, normal QT dispersion does not necessarily exclude substantial dispersion in local RT as an underlying factor of arrhythmogenesis. The explanation for this semiparadox is probably the fact that over 90% of all repolarization signals from the ventricles is cancelled in the surface ECG, as was described almost four decades ago by Burgess and colleagues (3). The duration of the T wave in the ECG reflects dispersion of the whole repolarization process in the whole heart, which is not the same as dispersion in the local moments of recovery from inexcitability (dispersion in complete RT). The latter parameter has been assessed previously in the epicardium of the human heart where it was reported that dispersion in RT is only 14 ms, whereas the dispersion in activation time is 23 ms (11). Therefore, repolarization seems a highly synchronized process despite the fact that the underlying signal (phase 3 or the repolarization phase of the ventricular action potential) is in itself very slow compared with the depolarizing fast upstroke of the action potential.

Thus far the dispersion in the end of the T wave but also the configuration of the T wave lack reasonable detailed explanations. Roughly, three types of repolarization inhomogeneities play a role: 1) differences between right and left ventricle, 2) differences between apex-base and anterior-posterior, and finally 3) transmural differences (6). The involvement of M cells in transmural dispersion is still a matter of debate (1, 2, 7, 18).

COMPARISON WITH OTHER STUDIES

The study of Chauhan et al. (5) shows overall RT dispersion of 17 and 51 ms along the RV endocardium and LV epicardium, respectively, in patients without VTs or TWA (see Fig. 2, bottom panel in Ref. 5). This epicardial value is somewhat higher than that observed in previous studies where it was 14 ms (11) or 41 ms (13) in patients with preserved LV function undergoing bypass surgery. It is suggested that this is due to the underlying cardiomyopathy. In patients with VTs or positive TWA the overall RT dispersion was 73 and 66 ms along the RV endocardium and LV epicardium, respectively. This is substantially more than previously reported (11,13), but it should be underscored that the underlying pathophysiology differs. Furthermore, whole dispersion in RT is sensitive to the dimensions of the area of assessment, and if the entire endocardium or epicardium has not been mapped, we may assume that the total RT is an underestimation of the real total RT in this study (and in other studies). There is no satisfactory explanation for the difference in dispersion in RT between the groups with and without VTs. It is probably not a coincidence that the difference in adjacent RT (10–12 vs. 2–3 ms/mm in the groups with and without VTs or TWA; see bottom panels of Figs. 2 and 3 in Ref. 5) was much larger than the differences in total RT between the two groups. It is tempting to ascribe this to wall motion abnormalities.

It has previously been shown that the dispersion in refractoriness of normal myocardium in patients with a healed myocardial infarction may determine the severity of an arrhythmia (16). Patients had either VT or ventricular fibrillation as the index arrhythmia. During subsequent surgical correction of the infarcted area, ventricular fibrillation was provoked by a battery. Dispersion of ventricular fibrillation intervals was twice as large in patients who had been presenting with ventricular fibrillation compared with patients in which the index arrhythmia had been restricted to VT. This underscores that dispersion in RT of normal myocardium adjacent to diseased myocardium plays a prominent role in arrhythmogenesis.

There is an increasing body of evidence that wall motion abnormalities do play an important role in the genesis of arrhythmias (10, 14) and that they increase dispersion in QTc intervals as well (17). There is, however, thus far no direct evidence that wall motion abnormalities also increase dispersion in ARIs and RTs. In the present study, wall motion abnormalities were not different between the two patient groups (see Table 2 in Ref. 5), although...
it should be emphasized that this study does not permit a direct assessment of the interaction, because there was no direct relationship between the areas of assessment of wall motion abnormality and of the electrophysiological measurements. Interestingly, ARIs as well as RTs tended to be shorter in patients with VTs or positive TWA (see Table 3 in Ref. 5) in addition to the differences in dispersion.

It is well known that ARIs tend to become shorter in the direction of propagation (6, 13). Thus when activation time increases, ARIs become increasingly shorter. With a slope of $-1$ between the two parameters, differences in activation time would be exactly compensated by differences in ARIs. If this happens in a whole heart, there would be no dispersion in repolarization and therefore no T wave. Comparison of the relationships between activation time and ARIs along the endocardium and epicardium in the two patient groups is given in Figs. 4 and 5 in the study of Chauhan et al. (5). On average, the correlation coefficients were $-0.65 \pm 0.08$ and $-0.66 \pm 0.14$ along the RV endocardium and LV epicardium of patients without VTs or TWA. In patients with VTs or positive TWA, these correlation coefficients were $-0.35 \pm 0.13$ and only $0.1 \pm 0.2$ along the RV endocardium and LV epicardium. Correlation coefficients are not the same as slopes of regression lines, and the authors provide us with values of $-0.7 \pm 0.1$ in patients without VTs or TWA along the RV endocardium and $-1.3 \pm 0.2$ along their LV epicardium. It seems as if the patients without a tendency to arrhythmias were still able to shorten ARI, whereas the patients with VTs or positive TWA were not, as is the case in patients with atrial fibrillation. Of course, the loss of this characteristic also increases dispersion in RT. It cannot be determined with certainty whether the increase in adjacent RT (larger on a distance scale, but smaller in absolute terms) or, alternatively, the increase in whole organ RT is the most important factor.

**FUTURE ASPECTS**

Chauhan et al. (5) mention that the repolarization proceeded from base to apex in about 60% of the patients along both endocardium and epicardium. Apparently, the direction of the repolarization front may vary. In addition, it is intriguing that there is a difference in endocardial versus epicardial RT. The point that the endocardial RTs were measured in the RV and the epicardial RTs on the LV is well taken, but still, as Chauhan et al. claim in their description of Fig. 1 of their study, the sites of measurement were adjacent. From the functional point of view, in terms of genesis of the T wave, it does not matter whether a signal arises from the LV or the RV. We emphasize that there was no difference between endocardial and epicardial RT in the patients without VT or TWA (288 vs. 287 ms, Table 3 in Ref. 5), whereas these numbers were 269 vs. 249 ms in patients with VT or TWA. One would expect that this has consequences for the configuration of the T wave in the two patient groups, but the present study does not provide us with this type of information. Janse and colleagues (15) recently described that there is no transmural gradient of repolarization in the intact canine left ventricle, and therefore it cannot be expected that this contributes to the configuration of the T wave or to dispersion in RT. There is sparse information that this also applies to the human heart (6, 8). There is a need for experiments that both unravel the repolarization of the human ventricle on a detailed scale as known for the activation and assess the impact of wall motion abnormality/mechanoelectrical feedback on the repolarization process including its dispersion. In the meantime the present study of Chauhan et al. (5) is important in corroborating the notion that dispersion in repolarization remains highly relevant for arrhythmogenesis in the human heart.

**REFERENCES**


