Europace (2007) **9**, 48–49

Letter to the Editor

doi:10.1093/europace/eul138

Biventricular pacing and transmural dispersion of the repolarization

In 2003, Medina-Ravell *et al*.[1] published a study that suggested that biventricular pacing could be arrhythmogenic in a subset of patients because of the reversal of the normal endocardial-to-epicardial activation sequence by left-ventricular epicardial pacing. As epicardial action potentials are briefer than endocardial action potentials, transmural dispersion of the repolarization (TDR) is larger with an epicardial-to-endocardial activation sequence than with an endocardial-to-epicardial activation sequence. Medina-Ravell *et al*. demonstrated this in an isolated arterially perfused rabbit left-ventricular wedge preparation. They also showed, in a quasi-ECG derived from this preparation, that TDR was faithfully reflected by the $T_{peak\text{-}end}$ interval and that $T_{peak\text{-}end}$ was larger with epicardial pacing than with endocardial pacing of the preparation. Their conclusion that a similar effect occurs in intact hearts in humans was substantiated by the observation that in 29 heart failure patients with a biventricular pacemaker, the $T_{peak\text{-}end}$ interval was larger during left-ventricular epicardial pacing than during right-ventricular endocardial pacing. However, no $T_{peak\text{-}end}$ values with sinus rhythm and with biventricular pacing were reported, due to measurement difficulties.

With interest, we read the recently published study by Santangelo *et al*.[2] They describe how left-ventricular, right-ventricular, and bi-ventricular pacing in heart failure patients influences a number of ECG indexes of ventricular dispersion of the repolarization, among others the $T_{peak\text{-}end}$ interval. Compared with sinus rhythm, the $T_{peak\text{-}end}$ interval increased with left-ventricular epicardial and with right-ventricular endocardial pacing, but it decreased with bi-ventricular pacing. The observations by Santangelo *et al*. confirm nicely the findings of our recent study[3] in which we evaluated, in a similar way, the effect of left-, right-, and bi-ventricular pacing on a set of ECG indexes thought to represent ventricular dispersion of repolarization, among which was $T_{peak\text{-}end}$. We also found the briefest $T_{peak\text{-}end}$ interval to occur with biventricular pacing.

What should be the conclusion from these observations? Medina-Ravell *et al*.[1] conclude that, in their patients, epicardial left-ventricular pacing increases TDR with respect to right-ventricular pacing, because the $T_{peak\text{-}end}$ interval is the largest with left-ventricular pacing. Santangelo *et al*.[2] conclude, among others, on the basis of the behaviour of the $T_{peak\text{-}end}$ interval, that left-ventricular and right-ventricular pacing increase TDR with respect to sinus rhythm, whereas bi-ventricular pacing decreases TDR. The implications of such a conclusion would be that any single-lead ventricular pacing, be it sole endocardial right-ventricular or sole epicardial left-ventricular pacing, would be undesirable because it increases TDR. It also implies that the thus-created disadvantageous situation can be turned to being advantageous by simultaneous biventricular pacing. Would that mean that the inversion of the endocardial-to-epicardial activation by epicardial left-ventricular pacing is undone by simultaneous right-ventricular pacing? The BELIEVE study,[4] in which 74 heart failure patients who were randomized to left-ventricular only or to bi-ventricular pacing were followed for 1 year, was not able to detect any evidence for a proarrhythmic effect of left-ventricular pacing.

Our conclusion, supported by computer simulations[3] is that the $T_{peak\text{-}end}$ interval in the ECG of intact humans is not reflecting TDR, in contrast to the $T_{peak\text{-}end}$ interval in the quasi-ECG made in the left-ventricular wedge-preparation. The surface ECG made from a whole heart and the quasi-ECG derived from a preparation of the left-ventricular free wall are not analogous because surface ECG electrodes record, from a distance, electrical activity in the whole heart; in the above studies, cancellation plays a prominent role.[5] The quasi-ECG is, however, recorded close to a small preparation in which cancellation plays virtually no role. The peak in the T-wave in the surface ECG reflects septal repolarization rather than, e.g., repolarization of the endocardium in the case of left-ventricular epicardial pacing.

Although it may well be true that in intact human hearts with left-ventricular and with biventricular pacing, TDR may be locally increased under the left-ventricular epicardial electrode, this is not reflected in the $T_{peak\text{-}end}$ interval on the surface ECG.

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doi:10.1093/europace/eul139

Relationship between transmural dispersion of repolarization, T_{peak}–T_{end} interval, and ventricular arrhythmias: reply

We thank Dr Swenne and his colleagues for their interest in our manuscript.[1] Transmural dispersion of repolarization (TDR) in the heart has been linked to a variety of arrhythmic manifestations.[2] Three electrophysiologically distinct cell types have been identified in the ventricular myocardium: endocardial, epicardial, and M cells. Differences in the time course of repolarization of these three ventricular myocardial cell types contribute prominently to inscription of the electrocardiographic T-wave.[3] In isolated ventricular wedge preparations, the peak of the T-wave was shown to coincide with epicardial repolarization and the end of the T-wave with repolarization of the M cells, so that T_{peak}–T_{end} provides a measure of TDR.[4] Some studies have suggested that although T_{peak}–T_{end} interval on the surface ECG may not be absolutely equivalent to TDR, this interval may provide an index of TDR and thus be helpful in forecasting risk for the development of life-threatening arrhythmias.[3–7] The method for T_{peak}–T_{end} interval measurement must also be established. Some authors measured T_{peak}–T_{end} interval from the earliest T_{peak} to the latest T_{end} on the 12-lead ECG;[8] others selected special leads such as II, V5, an average of all leads, or ambulatory ECG to analyse T_{peak}–T_{end} interval.[9–11] Further studies are clearly required in order to define the measurement of this ECG interval, which is better correlated with TDR in humans.

Our data showed that epicardial left-ventricular (LV) pacing alone increases ventricular heterogeneity of repolarization and the risk of malignant ventricular arrhythmias compared with biventricular pacing (BiV), probably because of reversal of the physiological endocardial-to-epicardial ventricular activation.

In the BELIEVE study,[12] in which 74 heart failure patients who were randomized to left-ventricular only or to bi-ventricular pacing were followed for 1 year, sudden cardiac death occurred in only two patients and comparable numbers of ventricular arrhythmia episodes were observed in LV and BiV groups. This study was not able to detect any evidence for a proarrhythmic effect of left-ventricular pacing, perhaps because most patients were treated with amiodarone.

We believe that further studies are needed to assess the influence of left-ventricular pacing on myocardial dispersion of repolarization and to evaluate whether LV pacing affects the prevalence of ventricular arrhythmias.

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