Potential Proarrhythmic Effects of Biventricular Pacing

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Resynchronization therapy involving right ventricular endocardial and left ventricular epicardial pacing improves cardiac output, quality of life, and New York Heart Association functional class in patients with congestive heart failure. Although a great deal of attention has been directed at showing the mechanical benefits and in fine-tuning the biventricular pacing configuration and protocol, little attention has been focused on the consequences of reversing the direction of activation of the left ventricular wall. Recent basic science and clinical studies have shown a proarrhythmic effect of reversing the direction of activation of the left ventricular wall. Reversal of the normal activation sequence prolongs the QT interval and increases the existing transmural dispersion of repolarization, creating the substrate and trigger for re-entrant arrhythmias under long QT conditions. A number of case reports of R-on-T extrasystoles and ventricular tachyarrhythmia induction as a result of biventricular pacing support this observation, and raise concern that biventricular pacing may be proarrhythmic in select cases, particularly when associated with a prolonged QT interval. Our focus in this review is on current understanding of transmural heterogeneity of repolarization that exists across the left ventricular wall, how this dispersion of repolarization is amplified as a consequence of reversal of the normal activation sequence, and how these basic experimental findings may apply to patients receiving cardiac resynchronization therapy. (J Am Coll Cardiol 2005;46:2340–7) © 2005 by the American College of Cardiology Foundation

Biventricular pacing significantly improves cardiac output, quality of life, and New York Heart Association functional class in patients with congestive heart failure receiving pharmacologic therapy. The incidence of sudden cardiac death remains high in cardiac resynchronization therapy patients (1), and a recent meta-analysis of existing clinical trials showed that neither all-cause mortality nor non-heart failure deaths are significantly reduced by cardiac resynchronization therapy alone (2). Results of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study show a significant reduction in mortality when cardiac resynchronization therapy is combined with an implantable defibrillator in patients with advanced heart failure (3), implicating ventricular arrhythmias in the mortality of some advanced heart failure patients receiving resynchronization therapy.

A recent report by Medina-Ravell et al. (4) further implicated polymorphic ventricular tachycardia (VT) as a complication of resynchronization therapy. They reported the development of torsades de pointes (TdP) in a heart failure patient whenever biventricular or epicardial pacing was instituted, but not when the stimulation mode was changed to endocardial pacing only. Most resynchronization therapy performed today involves the insertion of a right ventricular lead to pace the apex of the right ventricle and a left ventricular (LV) lead introduced into the coronary sinus to pace the epicardium of the LV. Little attention has been focused on the consequences of reversing the direction of activation of the LV wall.

Experimental studies have shown a proarrhythmic effect of reversing the direction of activation of the LV wall (4,5). Reversal of the normal sequence of activation prolongs the QT interval and greatly increases the existing transmural dispersion of repolarization (TDR), creating a substrate for re-entrant arrhythmias as well as a trigger in the form of an early afterdepolarization (EAD)-induced extrasystole under long QT conditions. A number of case reports of R-on-T extrasystoles and ventricular tachyarrhythmia induction as a result of biventricular pacing support this observation and raise concern that biventricular pacing may be proarrhythmic in select cases, particularly when associated with a prolonged QT interval (4,6). Our focus in this review is on the current understanding of transmural heterogeneity of repolarization that exists across the LV wall, how this heterogeneity is amplified as a consequence of reversal of the normal activation sequence, and how these basic experimental findings may apply to patients receiving cardiac resynchronization therapy.

METHODS FOR HUMAN STUDY

This review includes some new, original human data. In a series of 10 patients with chronic heart failure, we paced the epicardial and endocardial aspects of the LV wall at the time of implantation of a biventricular pacemaker to compare the effects of reversing the direction of activation of the ventricular wall on QT and TDR. Patients with New York
Heart Association functional class III/IV heart failure underwent implantation with a cardiac resynchronization device capable of independent right- and left-sided pacing (Contak Renewal-II, Guidant Corp., St. Paul, Minnesota), and electrophysiologic study perioperatively, as previously detailed (7). The pacing protocol was performed after written informed consent.

The epicardium of the LV free wall was initially paced at a cycle length of 600 ms through the epicardial electrode of the device, placed at the distal venous system. The endocardial aspect of the LV free wall was then paced at an adjacent site across the wall at the same cycle length using a deflectable 6-F catheter positioned with the aid of fluoroscopy. A 12-lead electrocardiogram (ECG) was recorded.

We established a close similarity of the QRS morphology of the ECG as a criterion for inclusion of the patients in the analysis. With this criterion, we selected 4 patients of the series of 10 patients for inclusion; averaged data from these 4 patients are presented.

CARDIAC VENTRICULAR HETEROGENEITY

Heterogeneity within the ventricular myocardium was not fully appreciated until approximately 15 years ago (8). Differences among epicardium, endocardium, and the mid-myocardial or M region have been described in the dog, cat, pig, guinea pig, rabbit, and human ventricular myocardium (see Antzelevitch and Fish [9] for review). The principal characteristic of the M cell is the ability of its action potential to prolong out of proportion to that of epicardium and endocardium in response to slowing of the heart rate and/or some agents that prolong the action potential (Fig. 1).

**Figure 1.** Preferential prolongation of M-cell action potential in response to a slowing of stimulation rate. Transmembrane recordings obtained from tissue slices isolated from epicardial (Epi), M, and endocardial (Endo) regions of the canine right and left ventricles at basic cycle lengths (BCLs) of 300, 1,000, 2,000, and 5,000 ms. Modified and reprinted, with permission, from Sicouri et al. (8).
ROLE OF ELECTRICAL HETEROGENEITY
IN THE INSCRIPTION OF THE T-WAVE OF THE ECG

Voltage gradients developing as a result of the different time course of repolarization of phases 2 and 3 in the three cell types are known to give rise to opposing voltage gradients on either side of the M region, thus contributing to the inscription of the T-wave (10). In the case of an upright T-wave, the epicardial response is the earliest to repolarize and the M-cell action potential is the latest. Full repolarization of the epicardial action potential coincides with the peak of the T-wave and repolarization of the M cells is coincident with the end of the T-wave. The duration of the M-cell action potential therefore determines the QT interval, whereas the duration of the epicardial action potential determines the QT peak interval.

The T peak–T end interval thus provides an index of TDR (5,10,11). The available data suggest that T peak–T end measurements might best be limited to precordial leads because these leads more accurately reflect TDR and that the end of the T-wave be measured as close to the isoelectric line as possible. Recent studies have also provided guidelines for the estimation of TDR in the case of more complex T waves, including negative, biphasic, and triphasic T waves (12). In these cases, the interval from the nadir of the first component of the T-wave to the end of the T-wave provides an approximation of TDR.

Figure 2. Mathematical simulation of effects of epicardial versus endocardial pacing on QT interval, T peak–T end (Tp–Te), and TDR. (Top) Homogeneous myocardium. QT interval, T peak–T end, and TDR are unchanged when pacing site is shifted from endocardium (Endo) (left) to epicardium (Epi) (right) (basic cycle length = 2,000 ms). (Bottom) Heterogeneous myocardium. QT interval, T peak–T end, and TDR all increase after reversal of direction of activation of the transmural cable. Modified and reprinted, with permission, from Fish et al. (5).
Although the clinical applicability of these concepts remains to be fully validated, significant progress toward validation of the T peak–T end interval as an index of TDR has been achieved. Recent studies suggest that the T peak–T end interval may be a useful index of transmural dispersion and thus may be prognostic of arrhythmic risk under a variety of conditions (13–20). Direct evidence in support of T peak–T end as a valuable index to predict TdP in patients with long QT syndrome was provided by Yamaguchi et al. (21). These investigators concluded that T peak–T end is more valuable than QTc and QT dispersion as a predictor of TdP in patients with acquired long QT syndrome. Shimizu et al. (17) showed that T peak–T end, but not QTc, predicted sudden cardiac death in patients

Figure 3. Effect of reversal of transmural sequence of activation in canine LV wedge preparation. Epicardial (Epi), endocardial (Endo), and M-cell action potentials and a transmural electrocardiogram were simultaneously recorded during endocardial (A) and epicardial (B) pacing at a basic cycle length of 2,000 ms. All numbers are in milliseconds. ECG = electrocardiogram; other abbreviations as in Figure 2. Modified and reprinted, with permission, from Fish et al. (5).

Figure 4. Cisapride (0.2 μmol/l) permits induction of torsades de pointes during epicardial (Epi) but not endocardial stimulation. Epicardial and M-cell action potentials and a transmural electrocardiogram were simultaneously recorded during endocardial (A) and epicardial (B) pacing of the canine left ventricular wedge preparation at a basic cycle length of 2,000 ms. A polymorphic ventricular tachycardia was induced by an extrastimulus delivered to epicardium at an S1–S2 interval of 204 ms (C). ECG = electrocardiogram; other abbreviations as in Figure 2. Modified and reprinted, with permission, from Fish et al. (5).
with hypertrophic cardiomyopathy. Watanabe et al. (22) showed that prolonged T peak–T end is associated with inducibility as well as spontaneous development of VT in high-risk patients with organic heart disease.

Thus, evidence is accumulating in support of the hypothesis that T peak–T end may provide a reasonable index of TDR, and that prolongation of T peak–T end may be associated with the creation of a substrate for re-entry leading to the development of polymorphic VT. Additional studies are clearly needed to validate and assess the value of this non-invasive index of electrical heterogeneity and its value in the assignment of arrhythmic risk.

CONSEQUENCE OF REVERSING THE DIRECTION OF ACTIVATION OF THE LV WALL ON TDR AND T PEAK–T END

The activation sequence of the myocardium can significantly alter the QT interval, T-wave morphology, TDR, as well as T peak–T end. Figure 2 illustrates the effects of shifting the site of stimulation from endocardium to epicardium in a mathematical model (5) depicting transmural conduction of an impulse in a homogeneous versus heterogeneous myocardium. In the case of a homogeneous myocardium, in which all cells are identical, activation of the string of cells from the endocardial end results in a positive QRS but a negative T-wave because the earliest tissue to depolarize is also the earliest to repolarize. Full repolarization of the endocardial action potential is coincident with the nadir of the T-wave, and full repolarization of the epicardial response coincides with the end of the T-wave.

Reversing the direction of stimulation simply changes the polarity of the QRS and T-wave, with no change in action potential duration (APD), QT interval, TDR, or T peak–T end. When the simulation is modified to incorporate epicardial, M, and endocardial cells with their unique APD characteristics, endocardial activation gives rise to concordant QRS and T waves, because of the different time course of repolarization of the three cell types. Under these conditions, the peak of the T-wave is coincident with full repolarization of epicardium and the end of the T-wave.
coincides with full repolarization of the M cells. Reversal of the transmural direction of activation leads to inversion of the QRS, but to a taller and wider positive T-wave. The QT interval, T peak–T end, and TDR increase when epicardium is activated, whereas APD remains unchanged throughout the myocardium. After epicardial stimulation, epicardium depolarizes and repolarizes earlier and the M cells depolarize and repolarize later, leading to prolongation of TDR and T peak–T end.

RESULTS FROM ARTERIALLY PERFUSED CANINE AND RABBIT WEDGE PREPARATIONS

Tests of the predictions of the mathematical model have been performed in ventricular wedge preparations. Figure 3 shows the effects of endocardial versus epicardial stimulation in the canine arterially perfused LV wedge. Epicardial, M, and endocardial action potentials were simultaneously recorded using floating microelectrodes, together with a transmural ECG. As in the computer simulation, APD is largely unaffected by reversal of the transmural sequence of activation. The TDR, T peak–T end, and QT interval were substantially increased with a shift of the stimulation site from endocardium to epicardium (5). Unlike the mathematical model, but consistent with the human recordings, this shift of the stimulation site also led to a broadening of the QRS. This effect was caused by the imposition of an additional delay of conduction between epicardium and mid-myocardium when the preparation was stimulated from epicardium. This delay contributes prominently to amplification of TDR and is thought to be attributable to the presence of a resistive barrier in the deep subepicardium (23). A wave front approaching from the endocardium can traverse this region of increased resistivity more rapidly and effectively than a point source resulting from epicardial stimulation in close proximity to the barrier. The region of increased tissue resistivity may in part be caused by the sharp shift in the orientation of cells in this part of the wall (23–26). Recent studies suggest that this region of the myocardium may also have a reduced density of connexin-43–mediated gap junctions (27,28).

Although reversal of the direction of activation leads to a substantial increase in TDR in both the canine and rabbit LV wedge models under control conditions, this increase is not enough to permit the development of TdP. However, under long QT conditions, the shift to epicardial activation is sufficient to increase TDR to the threshold for re-entry, which in the canine ventricular wedge is approximately 90 ms. Figure 4 shows the effects of 0.2 μM cisapride, a gastric promotility agent with I Kr blocking effects, in the arterially perfused canine LV wedge. The TDR and T peak–T end are 40 ms and 43 ms, respectively, during endocardial stimulation at a basic cycle length of 2,000 ms. Neither spontaneous nor stimulation-induced TdP was observed. However, stimulation from the epicardium at the same cycle length dramatically increased both the TDR and T peak–T end to 90 ms. Delivery of an extra stimulus to the epicardium at a coupling interval of 204 ms induced a polymorphic tachycardia.

Similarly, in the rabbit LV wedge 5 nM dofetilide creates a large transmural dispersion between the endocardium and the epicardium (Fig. 5) (29,30). It is noteworthy that in the adult rabbit, the entire endocardium displays M-cell characteristics. During endocardial stimulation at a basic cycle length of 4,000 ms, dofetilide–induced EADs arising in the endocardium fail to propagate transmurally. On reversal of the activation sequence, the EADs propagate successfully, triggering brief episodes of TdP. Facilitation of EADs after epicardial activation of the myocardium also contributes to the accentuation of TDR (29). In both of these examples, the increase in TDR is produced by the drug and further amplified by the reversal of the transmural activation sequence.

Figure 6. A 12-lead electrocardiogram recorded from a 72-year-old man with dilated cardiomyopathy. The patient was paced at a cycle length of 600 ms from either the endocardium (Endo) or an epicardial (Epi) site immediately across the lateral aspect of the left ventricular free wall. During endocardial pacing (left), the QT interval in lead V4 was 444 ms and the T peak–T end interval was 142 ms. Pacing from the epicardium increased these values to 454 ms and 178 ms, respectively, and augmented and widened the T-wave.
ENDOCARDIAL VERSUS EPICARDIAL PACING OF THE LV IN HUMANS

Figure 6 shows changes similar to those observed in the wedge and in the mathematical model in a patient with dilated cardiomyopathy. The epicardium of the LV free wall was paced at a cycle length of 600 ms through the epicardial electrode of a resynchronization device. The endocardial aspect of the LV free wall was then paced at an adjacent site. During endocardial pacing, the QT interval in lead V6 was 444 ms and T peak–T end was 142 ms in V6, the lead facing the myocardium in closest proximity to the pacing leads. When the pacing site was shifted to the epicardium, QT and T peak–T end increased to 454 ms and 178 ms, respectively. The similarity of the QRS morphology in the 12 leads suggests that the epicardial and endocardial leads were opposite from each other in the same region of the LV wall. With this as a criterion, we selected 4 out of 10 patients for analysis. The QT increased from 442.1 ± 6.7 ms to 464.7 ± 20.5 ms, and T peak–T end increased from 111 ± 15 to 138 ± 24 ms (p < 0.05; n = 4).

These findings provide evidence supporting the hypothesis that reversing the direction of activation of the ventricular wall amplifies TDR as well as evidence supporting the presence of significant transmural repolarization heterogeneity in the human heart.

Epicardial activation-induced amplification of TDR can lead to the development of TdP arrhythmias as reported by Medina-Ravell et al. (4). In the example shown in Figure 7, endocardial pacing was not associated with any form of arrhythmic activity; QT interval was 485 ms and T peak–T end was 92 ms. Soon after switching to epicardial pacing, extrasystolic activity developed, giving way to an episode of TdP; QT interval increased to 580 ms and T peak–T end to 133 ms. The TdP was terminated by an implantable cardioverter-defibrillator shock. Biventricular pacing led to similar R-on-T extrasystoles and TdP in this patient.

Thus, this patient had a prolonged QT interval and moderate T peak–T end interval during endocardial stimulation that was not arrhythmogenic. With epicardial pacing, these parameters were amplified to create the substrate and trigger for the development of TdP. Although reversal of the direction of activation of the LV wall may not be arrhythmogenic by itself, it may play an important role in promoting arrhythmogenesis when combined with predisposing factors, such as QT prolongation, commonly associated with an already-prolonged TDR.

FUTURE DIRECTIONS

The available data point to epicardial activation of the LV wall during resynchronization therapy as a potential iatrogenic factor in a subset of patients predisposed to QT prolongation and other conditions in which TDR is prolonged. It is noteworthy that accentuation of TDR with epicardial activation contributes to the development of polymorphic VT, but not monomorphic VT because of different underlying mechanisms. Our experimental observations suggest that the potentially arrhythmogenic substrate can be avoided by stimulation of LV endocardium or possibly by using a screw-in lead to stimulate the mid-myocardium of the LV free wall. The latter is likely to reduce TDR and produce an antiarrhythmic effect.

Figure 7. Pacing site-dependent changes in QT interval, R-on-T ventricular extrasystoles, and the onset of torsades de pointes (TdP). Right ventricular endocardial pacing (RVEndoP; RR interval of 840 ms) yielded a QT interval of 485 ms and a T peak–T end interval of 92 ms. After switching to left ventricular epicardial pacing (LVEpiP; mode VOO), the QT interval increased to 580 ms and T peak–T end to 133 ms. Ventricular extrasystoles appeared at the 46th beat of LVEpiP (B) and initiated one episode of TdP after the 55th beat (C). The TdP was terminated by an implantable cardioverter-defibrillator shock. Modified and reprinted, with permission, from Medina-Ravell et al. (4).
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