Effect of Epicardial or Biventricular Pacing to Prolong QT Interval and Increase Transmural Dispersion of Repolarization

Does Resynchronization Therapy Pose a Risk for Patients Predisposed to Long QT or Torsade de Pointes?

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Background—The present study examined pacing site–dependent changes in QT interval and transmural dispersion of repolarization (TDR) and their potential role in the development of torsade de pointes (TdP).

Methods and Results—In humans, the QT interval, JT interval, and TDR were measured in 29 patients with heart failure during right ventricular endocardial pacing (RVEndoP), biventricular pacing (BiVP), and left ventricular epicardial pacing (LVEpiP). In animal experiments, pacing site–dependent changes in ventricular repolarization were examined with a rabbit left ventricular wedge preparation in which action potentials from endocardium and epicardium could be simultaneously recorded with a transmural ECG. In humans, LVEpiP and BiVP led to significant QT and JT prolongation. LVEpiP also enhanced TDR. Frequent R-on-T extrasystoles generated by BiVP and LVEpiP but completely inhibited by RVEndoP occurred in 4 patients, of whom 1 developed multiple episodes of nonsustained polymorphic ventricular tachycardia and another suffered incessant TdP. In rabbit experiments, switching from endocardial to epicardial pacing produced a net increase in QT interval and TDR by 17±5 and 22±5 ms, respectively (n=6, P<0.01), without parallel increases in ventricular transmembrane action potential durations. Epicardial pacing facilitated transmural propagation of early afterdepolarization, leading to the development of R-on-T extrasystoles and TdP in the presence of action potential duration–prolonging agents.

Conclusions—LVEpiP and BiVP increase QT, JT, and TDR by altering the transmural sequence of activation of the intrinsically heterogeneous ventricular myocardium. Our data suggest that the resultant exaggeration of arrhythmic substrates can lead to the development of TdP in a subset of patients. (Circulation. 2003;107:740-746.)

Key Words: pacing ■ ventricles ■ torsade de pointes ■ long-QT syndrome

Congestive heart failure (CHF) affects nearly 5 million Americans and claims more than 300 000 lives annually.1 Biventricular pacing (BiVP) is gaining popularity as an adjunctive therapy to pharmacological treatments in patients with severe CHF and intraventricular conduction delay. Many studies have demonstrated that BiVP in patients with advanced CHF significantly improves ventricular hemodynamics, quality of life, and exercise capacity.2–4

On the other hand, despite marked improvement in left ventricular pump function and the potential for decreased mortality by BiVP,5 the incidence of sudden cardiac death, which is likely attributable to the development of malignant ventricular arrhythmias,6 remains high.7–11 The common design for BiVP, ie, simultaneous pacing in right ventricular endocardium and left ventricular epicardium, is associated with a nonphysiological ventricular activation sequence that may augment transmural heterogeneity of repolarization intrinsic to ventricular myocardium and as a consequence prolongs the QT and JT intervals on the ECG. The present study tests this hypothesis by assessing the effects of BiVP, left ventricular epicardial pacing (LVEpiP), and right ventricular endocardial pacing (RVEndoP) on ventricular repolarization, specifically on QT and JT interval and transmural dispersion of repolarization (TDR), and their roles in arrhythmogenesis in patients who received resynchronization therapy. The cellular mechanisms underlying the pacing site–dependent alterations in ventricular repolarization were also studied in an experimental model consisting of an arterially perfused rabbit left ventricular wedge preparation in which transmembrane action potentials from endocardium and epicardium could be simultaneously recorded with electrocardiograms (ECGs) to assess the effects of BiVP and RVEndoP on the QT interval and TDR. The present study tests this hypothesis by assessing the effects of BiVP, left ventricular epicardial pacing (LVEpiP), and right ventricular endocardial pacing (RVEndoP) on ventricular repolarization, specifically on QT and JT interval and transmural dispersion of repolarization (TDR), and their roles in arrhythmogenesis in patients who received resynchronization therapy. The cellular mechanisms underlying the pacing site–dependent alterations in ventricular repolarization were also studied in an experimental model consisting of an arterially perfused rabbit left ventricular wedge preparation in which transmembrane action potentials from endocardium and epicardium could be simultaneously recorded with electrocardiograms (ECGs) to assess the effects of BiVP and RVEndoP on the QT interval and TDR.
cardium could be simultaneously recorded together with a transmural ECG.

**Methods**

**In Humans**

Twenty-nine consecutive patients (23 men and 6 women with a mean age of 71±8 years) with ischemic (n=23) or nonischemic (n=6) cardiomyopathy in NYHA class III/IV CHF (ejection fraction, 23±7%) underwent resynchronization therapy. Patients maintained chronic medications, including ACE inhibitors, diuretics, digoxin, and β-blockers to the time of biventricular pacemaker implantation. Eight of 29 patients had been taking low doses of amiodarone (200 to 400 mg once a day). None of the patients had a history of polymorphic ventricular tachycardia (VT) or torsade de pointes (TdP). The right ventricular lead was placed in the right ventricular apical endocardium, and the left ventricular lead was placed in an epicardial vein (lateral vein, n=10; posterolateral vein, n=17; and posterior vein, n=2) via coronary sinus access similar to the methods described by others.4

The data were collected perioperatively (n=29) 24 hours after the operation (n=19) and during the first follow-up period, ranging from 1 to 2 weeks after the procedure (n=12). No significant difference was found among the data collected at different intervals. The QRS duration, QT interval, JT interval, and TDR in patients were measured by 3 blinded observers. The QT interval was defined as the time interval between the initial deflection of the QRS and the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line. Similarly, the JT interval that excludes the QRS component was measured as the time from J point to the end of the T wave. TDR was defined as the interval between the peak to the end of the T wave (Tpeak-end).12,13 However, Tpeak-end was not estimated at baseline and during BiVP because of flattened T waves in most patients studied.

To minimize the influence of heart rate on the correction of QT interval, JT interval, and TDR, pacing rate was kept constant during RVEndoP, BiVP, and LVEpiP in each individual patient. The QT interval, JT, QRS, and TDR were compared using the measurements from the same leads among RVEndoP, BiVP, and LVEpiP. Corrected QT (QTc), JT (JTc), and TDR (TDRc) were calculated using Bazett’s formula.

**In Animal Experiments**

The methods used for isolation, perfusion, and recording of transmembrane activity from the arterially perfused rabbit left ventricular transmural wedge were detailed in previous studies.14 briefly, transmural wedge preparations with a dimension of ~2×1.5×0.5 cm were dissected from rabbit left ventricles and cannulated via the circumflex coronary artery and perfused with Tyrode’s solution (35.7±0.2°C). Transmembrane action potentials in wedge preparations were recorded simultaneously from epicardial and endocardial sites using 2 separate intracellular floating microelectrodes. A transmural ECG was recorded concurrently. Action potential duration (APD) was measured at 90% repolarization (APD90). TDR was defined as the difference between the longest and shortest repolarization times across left ventricular wall. This is closely approximated by Tpeak-end.12

**Statistics**

Statistical analysis of the data was performed using Student’s t test for paired data or one-way ANOVA coupled with Scheffé’s test among three or more groups. χ² test was used for the comparison between two groups for event incidences. Data are presented as mean±SD.

**Results**

**Pacing Site–Dependent Changes in Ventricular Activation and Repolarization in Patients**

In the present study, the patients demonstrated a significant baseline ventricular activation delay with an average QRS duration at 154±19 ms attributable to left bundle-branch block (n=14), intraventricular conduction delay (n=13), and right bundle-branch block (n=2). BiVP resulted in a small but statistically significant reduction in patients’ QRS duration (144±19 ms during BiVP versus 154±19 ms at baseline, n=29, P<0.05). RVEndoP and LVEpiP, on the other hand, led to a marked prolongation in ventricular activation time (Figure 1).

The patients’ baseline QTc was 468±38 ms. The effects of pacing site on QT interval are shown in Figure 2. The QT interval during LVEpiP was significantly longer than that during RVEndoP and BiVP. QTc during LVEpiP was 587±55 versus 544±36 ms during RVEndoP and 535±38 ms during BiVP (n=29, P<0.01). Because the QTc duration was significantly longer during RVEndoP and LVEpiP than at baseline and during BiVP (Figure 1), the QT intervals during RVEndoP and LVEpiP were probably overcorrected by using Bazett’s formula, particularly at pacing rates >60 ppm. In other words, BiVP-dependent ventricular repolariza—
tion delay may be masked by relatively briefer QRS duration. The latter was supported by the data that the JTc interval during BiVP (350 ± 32 ms) was moderately shorter than that during LVEpiP (359 ± 34 ms) but significantly longer than that during RVEndoP (302 ± 27 ms, Figure 2). TDRc was significantly greater during LVEpiP than during RVEndoP (197 ± 26 versus 163 ± 25 ms, n = 29, P < 0.01).

**Pacing Site–Dependent R-on-T Extrasystoles, Polymorphic VT, or TdP in Patients**

In 4 of 29 patients, BiVP/LVEpiP, which caused a marked increase in JTc (306 ± 35 ms in RVEndoP versus 382 ± 43 ms in BiVP) and TDR (149 ± 19 ms in RVEndoP versus 220 ± 33 ms in LVEpiP), resulted in frequent R-on-T ventricular extrasystoles that were completely inhibited by RVEndoP. One developed recurrent nonsustained polymorphic VT, another suffered incessant TdP requiring multiple electrical shocks. Figure 3 demonstrates the development of TdP during BiVP or LVEpiP in a male patient with idiopathic cardiomyopathy (ejection fraction, 18%). He underwent a single-chamber ICD and a dual-chamber pacemaker implantation 4 years previously because of inducible monomorphic VT and A-V block. The patient’s system had been recently upgraded to BiVP therapy. Approximately 3 to 4 hours after BiVP, the patient developed 13 episodes of sustained TdP and received the same number of shocks from his ICD (Figure 3). Serum electrolytes were all within normal range. Intravenous amiodarone was started after the first episode of TdP, but it failed to suppress it. After recognizing that QT prolongation and TdP were solely pacing site–dependent, amiodarone was discontinued, and the patient’s device was then programmed to RVEndoP. No new episodes of TdP occurred overnight during RVEndoP. BiVP was resumed the next morning after an event-free night. Numerous episodes of sustained TdP and nonsustained TdP reoccurred 4 hours later. Again, switching to RVEndoP completely and immediately suppressed TdP.

**Figure 3.** A, Incessant R-on-T ventricular ectopic beats and TdP were observed in a patient 3 to 4 hours after biventricular pacer implantation. Note that R-on-T extrasystoles were adequately sensed by the device. B, Typical episode of TdP during BiVP that was terminated by an ICD shock.

**Figure 4.** Pacing site–dependent changes in QT interval, R-on-T ventricular extrasystoles, and the onset of TdP. RVEndoP (RR interval of 840 ms) yielded a QT interval of 485 ms. Immediately after switching to LVEpiP (mode VOO), the QT interval increased to 580 ms (A). Ventricular extrasystoles started at the 46th beat of LVEpiP (B) and initiated one episode of TdP at the 55th beat (C) that was terminated by an ICD shock. Switching from RVEndoP to BiVP resulted in an increase in QT interval by 56 ms accompanied by R-on-T ventricular extrasystoles (D).
and extrasystoles. The patient was then discharged from the hospital with RVEndoP on a low dose of amiodarone (200 mg/d) and returned for follow-up 10 days later without any TdP events. In the office, the patient’s device was reprogrammed from RVEndoP to BiVP and to LVEpiP. As shown in Figure 4, switching from RVEndoP to LVEpiP or BiVP was associated with marked QT prolongation and frequent R-on-T extrasystoles, leading to the development of TdP (Figure 4, A through D).

**Pacing Site–Dependent Changes in Ventricular Repolarization and Their Role in Arrhythmogenesis in Rabbit Left Ventricle**

The effects of epicardial and endocardial pacing on QT interval, transmembrane APD, and TDR were examined in the isolated arterially perfused rabbit left ventricular wedge preparations and summarized in the Table. As shown in Figure 5, switching from endocardial to epicardial pacing resulted in a change in activation sequence between epicardium and endocardium that was associated with an increase in QT interval and TDR without a parallel increase in endocardial and epicardial transmembrane APD. An increase in TDR manifested as a more positive and broad T wave, as shown in the right panel of Figure 5. In a total of 6 preparations, switching from endocardial to epicardial pacing produced a net increase in QT and TDR by 17±5 and 22±5 ms, respectively, at a BCL of 1000 ms (P=0.05, Figure 6). An APD-prolonging agent, dofetilide (5 to 10 nmol/L), significantly prolonged QT and TDR, and epicardial pacing exaggerated the effect of dofetilide (Figure 6, Table).

When the preparations were perfused with dofetilide, phase 2 early afterdepolarization (EAD) appeared in endocardium but failed to propagate transmurally during endocardial pacing at BCLs of 2000 to 4000 ms (Figure 7A). Switching from endocardial to epicardial pacing facilitated transmural propagation of EAD, leading to the development of R-on-T extrasystoles (Figure 7B). In the fixed pacing period, the number of R-on-T extrasystoles and episodes of TdP induced by EAD was significantly greater during epicardial pacing than during endocardial pacing (301 versus 97, P<0.05, Table). A similar result (data not shown) was obtained in the experiments with administration of sotalol (30 μmol/L, n=3).

**Discussion**

In the present study, we provide for the first time clinical and experimental evidence that a pacing site–dependent change...
in ventricular activation sequence can lead to alterations in ventricular repolarization in electrically heterogeneous ventricular myocardium. QT or JT prolongation and an increase in TDR during LVEpiP and BiVP could facilitate the development of TdP.

For an apparent and obvious pacing site–dependent change in QT interval in patients, one would first speculate that a change in pacing sites per se might induce a change in ventricular transmembrane APD. The data obtained from the rabbit ventricular wedge preparation in the present study (Figure 5), however, demonstrated that a pacing site–dependent increase in QT interval and TDR occurred in the absence of transmembrane APD prolongation in epicardium and endocardium.

Theoretically, if APD in all ventricular myocardial layers were uniform, the QT or JT intervals would be constant regardless of pacing sites as long as the activation time (the QRS duration) was not altered. However, ventricular myocardium is not uniform but rather comprised of electrophysiologically distinct cell types in terms of their repolarization properties.12,16 Normally, ventricular activation starts with endocardium via subendocardial Purkinje network and spreads across the ventricular wall. Although the epicardium is activated last, it repolarizes first because of its shorter APD, producing a repolarization sequence opposite to activation.12 On the ECG, such an activation and repolarization sequence produces an upright T wave with the same polarity as the QRS.12 In other words, the QT interval is normally determined by the myocardial layers with the longest APD located in subendocardium or endocardium.12,16 Therefore, anything that alters ventricular activation sequence and delays activation in subendocardium and endocardium would prolong QT interval. This is supported by the finding from the present study that epicardial pacing delayed activation in endocardium (Figure 5), where APD was significantly longer than that of epicardium, leading to QT prolongation. If this is the case in human ventricles, LVEpiP could produce more significant QT prolongation in humans than in rabbits because of longer ventricular activation time, particularly under conditions of intraventricular conduction delay in humans. The QT interval during BiVP is more complicated because there are two activation as well as repolarization vectors. The fact that the JT interval during BiVP is longer than during RVEndoP but shorter than during LVEpiP suggests a moderate ventricular repolarization delay during BiVP.

Similarly, a change in pacing site would also influence TDR via the alteration in ventricular activation sequence.
Interestingly, a more marked increase in TDR than in QT interval was observed during epicardial pacing. This was largely attributable to the fact that an increase in TDR was determined not only by the delayed activation in subendocardium and endocardium (longer APD) but also earlier activation in epicardium (shorter APD). Therefore, it is a significant increase in TDR, rather than APD or QT prolongation, that provides the substrate for the development of TdP.17

One may argue whether it matters if a pacing site–dependent increase in QT or JT prolongation and TDR is not associated with a real change in transmembrane APD. Our data obtained from the rabbit left ventricular wedge preparation indicate that the pacing site–dependent increase in the QT interval and TDR may not be of consequence under normal conditions or in the absence of other risk factors for polymorphic VT and TdP. However, a pacing site–dependent increase in the QT interval and TDR could be arrhythmogenic in patients who have risk factors for QT prolongation, eg, nonischemic dilated cardiomyopathy or use of APD-prolonging agents. In a recent study by Cazeau et al,4 two patients died shortly after BiVP. Similar observations have been made by others.10,11,18 Although the exact cause for those sudden cardiac deaths during BiVP is unknown, pacing site–dependent TdP secondary to ventricular repolarization delay and enhanced TDR should be considered. Electrophysiological abnormalities in CHF, particularly in nonischemic cardiomyopathy per se, include spontaneous EAD and increased TDR, known risks for the development of TdP.16 LVEpiP and BiVP may increase the risk for TdP in patients with CHF by exaggerating TDR. Enhanced TDR increases the risk for the development of TdP, probably via two mechanisms. First, it facilitates transmural EAD propagation leading to R-on-T ventricular extrasystoles capable of initiating TdP, as shown in Figure 7B. Second, it could serve as a reentrant substrate for the maintenance of TdP,12,13 Therefore, BiVP/LVEpiP may increase the risk of TdP significantly in clinical scenarios that are only associated with the genesis of EAD, such as nonischemic cardiomyopathy or use of QT prolonging agents or ventricular rate drops with short-long-short cycles (Figures 4A through 4C). In contrast, RVEndoP, in which the ventricular repolarization gradient is reversed with epicardium repolarizing last, would be expected to suppress transmural propagation of EAD from subendocardium or endocardium to epicardium and therefore prevent the development of TdP.

Whether BiVP reduces ventricular arrhythmias is still a matter of controversy. Some studies have shown that BiVP is associated with a decrease in the incidence of monomorphic VT or its inducibility.19–21 In the study by Higgins et al.,19 however, the mortality during BiVP remained high despite the diminished antitachycardia therapy for monomorphic VT. Regardless, no data are available on the effects of BiVP and LVEpiP on the incidence of polymorphic VT and TdP. It is well known that the mechanisms underlying monomorphic VT are different from those responsible for polymorphic VT or TdP. Most monomorphic VT can be initiated by any type of ventricular beat and can be maintained via a fixed reentrant circuit, eg, ventricular scar. On the other hand, polymorphic VT or TdP is often initiated by an R-on-T extrasystole and maintained by a functional reentrant circuit, eg, enhanced TDR.

**Basic and Clinical Implications**

It is generally accepted that there is an intrinsic repolarization difference among epicardium, M cells, and endocardium. However, it remains controversial whether such an intrinsic repolarization difference among 3 cell types could be expressed in ventricles in vivo in which cell-to-cell is electrically coupled.13,22–24 In other words, is repolarization across the ventricular wall uniform or heterogeneous? A confounding variable in previous clinical attempts to quantify TDR in humans has been the presence of anesthetics and other agents known to reduce this parameter. The data obtained in the present study provide compelling evidence for the presence of significant transmural dispersion of repolarization in the unanesthetized human heart.

From the clinical perspective, a BiVP- or LVEpiP-dependent increase in QT interval and TDR may be a potential risk for the development of TdP in a subset of patients. It should be emphasized, however, that the overall incidence of TdP during BiVP and LVEpiP would be low. This is because a change in pacing sites may facilitate the development of TdP only under conditions in which a trigger (eg, EAD) and enhanced TDR are present. Risk stratification for TdP should be performed by 24 hours of postoperation telemetry monitoring, particularly in those patients on APD-prolonging drugs and those with nonischemic cardiomyopathy, to detect BiVP- or LVEpiP-dependent QT prolongation, ectopic ventricular extrasystoles, and TdP. The ICD may be an important component of therapy for these high-risk patients.

**Acknowledgments**

This work was supported by a Grant-in-Aid from the American Heart Association, the Adolph and Rose Levis Foundation, the Fourjay Foundation, and the Sharpe Foundation.

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_Circulation_. 2003;107:740-746; originally published online January 20, 2003;
doi: 10.1161/01.CIR.0000048126.07819.37
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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