A Mechanism of Torsades de Pointes in a Canine Model

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SUMMARY A dog model of torsades de pointes (TdP) was developed. Twenty 18–30-kg dogs had cardiopulmonary bypass initiated to maintain stable temperature, perfusion pressure and oxygenation. Quinidine, 30 mg/kg, was then administered and burst ventricular pacing was used to induce arrhythmias. The left anterior descending coronary artery was occluded for 15 minutes and repeat pacing studies were performed. Maps of epicardial activation were made from 27 simultaneously recorded electrograms obtained from 1-mm bipolar electrodes secured to the epicardium with a nylon mesh sock. Arrhythmias in five dogs met criteria for the diagnosis of TdP: All had the characteristic undulating QRS morphology typically associated with TdP, all occurred in the setting of QT prolongation and all ended spontaneously. The epicardial maps demonstrated that each change in QRS morphology was associated with a change in the site of epicardial breakthrough. Those QRS complexes during the transition from one morphology to the next were associated with fusion cycles in which both the old and new sites of epicardial breakthrough were present. In essence, two or more competing activation sequences were vying for control of epicardial depolarization. This conclusion was strengthened by our ability to simulate TdP in the surface ECG and in epicardial maps by simultaneously pacing from two widely separated ventricular sites at slightly different, varying rates.

TORSADES DE POINTES (TdP) is a ventricular arrhythmia seen in the setting of QT prolongation.\(^1\)\(^-\)\(^5\) It has been associated with a wide array of clinical entities, including congenital QT prolongation,\(^5\)\(^,\)\(^6\) atrioventricular block,\(^3\)\^-\(^5\)\(^,\) quinidine intoxication,\(^8\) hypokalemia\(^5\)\^-\(^9\)\(^,\)\(^10\) and myocardial infarction.\(^11\) Morphologically, it is characterized by an undulating QRS with peaks that appear to rotate gradually around an isoelectric baseline, as if the entire run were housed in a sinusoidal envelope.\(^12\) TdP is also known for its pernicious nature and for its responsiveness to isoproterenol\(^1\)\^-\(^3\)\(^,\)\(^5\)\^-\(^9\)\(^,\)\(^13\) and to overdrive suppression pacing.\(^1\)\^-\(^3\)\(^,\)\(^5\)\(^-\)\(^14\)

The underlying electrophysiology of TdP is not known. When Dessertenne originally described the arrhythmia in 1966 in an 80-year-old female with complete atroventricular block, he favored the theory that two competitive automatic ventricular pacemakers were alternately controlling the heart.\(^12\) Since then, others have advanced different explanations, but none has provided definitive evidence of the epicardial activation sequence underlying TdP. We developed a canine model of TdP to better define its epicardial activation sequence in a controlled laboratory setting with the aid of epicardial mapping.

Methods

A ventricular arrhythmia was diagnosed as TdP if it satisfied three criteria:\(^15\)\^-\(^16\) It had to be composed of groups of QRS complexes that gradually changed polarity in an undulating fashion; it had to occur in the setting of QT prolongation; and it had to terminate spontaneously. Five dogs yielded 19 runs of TdP that satisfied these criteria.

Figure 1 is a diagram of the experimental procedure. TdP induction was attempted in 20 mongrel dogs that weighed 18–30 kg. The dogs were anesthetized with sodium pentobarbital, 30 mg/kg, and ventilated through a Harvard respiration pump (model 607). A median sternotomy was performed and the heart was suspended in a pericardial cradle. Mean arterial pressure was monitored from the left femoral artery with a Gould P23 ID Stranchnum pressure transducer through a Hewlett Packard pressure amplifier (model 805C) and viewed on a Tektronix Oscilloscope Display Screen (model 7613). The left anterior descending coronary artery (LAD) was loosely encircled with a 4–0 silk ligature immediately distal to the first anterolateral branch for subsequent occlusion. Because TdP is highly prone to degenerating into ventricular fibrillation, cardiopulmonary bypass was instituted to help stabilize already precarious compromised dogs. Cardiopulmonary bypass was established with a bypass pump (Sarns Incorporated) and a Shiley 100A blood oxygenator. Venous return to the oxygenator was through a Bardic 38-gauge cannula inserted into the right atrium. Blood was returned to the dog through a 16-gauge cannula in the right femoral artery.

Epicardial recordings were made from 26 bipolar electrodes separated from each other by 1 mm and secured to the epicardium in a nylon mesh sock.\(^17\) A bipolar epicardial reference electrode was sutured to the left ventricular epicardium. To ensure a normal, stable core cardiac temperature throughout the experiment, myocardial temperature was monitored with an Instrumentation Laboratory thermistor (catalog 44910) inserted into the interventricular septum. Temperature was adjusted with the bypass pump as necessary. Rapid ventricular pacing was performed from three sites with bipolar hook electrodes constructed from Teflon-
coated silver wires and plunged through the ventricles with a 19-gauge needle, which was then withdrawn, leaving the silver wires lodged against the endocardium. Electrogroms from limb leads I, II and III were then simultaneously recorded at a paper speed of 100 mm/sec and baseline QT intervals were measured as the interval between the earliest QRS deflection and the terminal part of the T wave from the limb lead demonstrating the longest QT interval. Quinidine was administered over 15 minutes at a loading dose of 30 mg/kg, followed by a constant infusion of 5.6 μg/kg/min. This dose was chosen to produce toxic quinidine levels according to known pharmacokinetics modified for expected changes in the volume of distribution as a result of cardiopulmonary bypass. Blood samples were obtained at the end of the study to determine quinidine levels by photofluorometric precipitation. Burst pacing from the right ventricular outflow tract, the right ventricular apex and the left ventricular free wall near the base was done with eight-beat salvos delivered with a stimulus strength twice diastolic threshold. Stimuli were initially delivered with a cycle length of 250 msec and then decreased in 5-msec decrements until a rapid ventricular arrhythmia resulted or the pacing stimulus failed to capture the ventricle on a one to one basis. If no ventricular arrhythmia could be induced from any of the three pacing sites, the LAD was occluded; after 15 minutes, the pacing protocol was repeated. At the end of the study, QT intervals were again recorded as described above.

Electrocardiographic limb leads I, II and III and 27 bipolar epicardial signals were recorded continuously on a 32-channel FM analog tape recorder (Ampex PR-220). The epicardial potentials recorded during ventricular arrhythmias were played back from the tape recorder, digitized and entered in a computer (Digital Equipment Corporation PDP-11/34) as described elsewhere. Local activation times at each electrode were determined for each ventricular cycle. The activation times for each bipolar electrogram are preliminarily chosen by the computer and displayed on a Tektronix 4014 graphics terminal. All computer-chosen activation times are then reviewed by the investigator for accuracy. Adjustments can be made by hand if necessary. Once the position of each bipolar electrode is designated on the epicardial map for the computer, isochrones of epicardial activation can be constructed by the computer using previously chosen local activation times. Isochronous maps of epicardial activation can then be displayed on the Tektronix graphics terminal. Details of this analysis have been described.

In two dogs, TdP was simulated by pacing at different rates from two widely separated endocardial sites. Stimuli were delivered through bipolar plunge electrodes. One electrode was secured at the right ventricular endocardium and the other at the left ventricular endocardium. Each site was paced with a stimulus strength of 2 mA and a pulse width of 4 msec. The right ventricular site was paced at a constant cycle length of 180 msec. Cycle length at the left ventricular site was gradually changed from 165 to 195 msec and back to 165 msec.

Results

Five of the 20 dogs yielded runs of a ventricular arrhythmia that met the criteria for TdP. From these five studies, 19 runs of TdP were recorded and analyzed. All five dogs had prolonged QT intervals after quinidine compared with baseline recordings (table 1). The mean QT interval was 0.21 ± 0.01 second (± SD) before and 0.27 ± 0.04 second after quinidine administration (p = 0.016 by paired t test). The mean quinidine level in these five dogs was 6.4 mg/l. The normal QT interval for dogs has been reported as 0.177 ± 0.054 second and 0.21 ± 0.02 second. The duration of TdP ranged from 2.7 to 160 seconds (12–820 cycles) (mean 43 ± 46 seconds). All runs terminated spontaneously. TdP was induced in one dog with quinidine alone (quinidine level of 4.6 mg/l), but the

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Before = before quinidine or occlusion; After = after quinidine and occlusion.
other four dogs required LAD occlusion as well as quinidine before TdP could be induced. In eight runs, a typically uniform run of ventricular tachycardia was intermingled with TdP.

Of the 15 dogs that failed to manifest TdP, 12 had a prolonged QT interval of at least 20% over baseline. These 15 dogs without TdP did, however, yield monomorphic ventricular tachycardia, ventricular fibrillation or both. All runs of monomorphic ventricular tachycardia manifested only one site of epicardial breakthrough during epicardial activation mapping. We do not know why these dogs did not develop TdP.

Isochronous maps of TdP revealed that epicardial activation occurred in discrete cycles and that each

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**Figure 2.** Correlation of isochronous maps of epicardial activation with changes in QRS morphology during torsades de pointes. Every other cycle is presented through a typical transition from one QRS morphology to another and back to the first again. Each panel demonstrates the map of the cycle identified by the arrow in limb lead II. The heart is presented as if cut from apex to crux along the posterior interventricular groove and then flattened. Each number represents local activation time (msec) relative to the point of earliest epicardial breakthrough, which is indicated by zero. Isochrones are shown every 10 msec and estimate the location of the depolarization front at one instant during excitation. The asterisks denote the location of recording electrodes over ischemic myocardium that failed to register discrete epicardial activation. (A) Epicardial activation is primarily controlled from a site that breaks through on the basilar anterior left ventricular surface. A second, relatively early site is at the apex 41 msec after earliest epicardial breakthrough. (B) Epicardial activation undergoes subtle changes near the inferior margin of the infarct. (C) Transition complex. Simultaneous epicardial breakthrough occurs from the basilar and apical left ventricle (LV). Note the associated change in the QRS morphology in limb lead II. (D) The apical location captures complete control of epicardial depolarization, with the high anterior LV no longer demonstrating early breakthrough. (E) There is a gradual lengthening in total duration of epicardial activation, but the pattern of activation is generally unchanged. (F) The site of earliest epicardial breakthrough shifts slightly from the apex to the posterior LV, with a small change in the QRS morphology as seen in limb lead II. (G) The basilar anterior LV site of epicardial breakthrough reappears near simultaneously with the apically located site of earliest breakthrough. At this point, QRS morphology dramatically changes and appears to be transitional between the two basic morphologies. (H) The basilar anterior LV site resumes predominant control of epicardial depolarization and the limb lead QRS is upright again. RV = right ventricle; PA = pulmonary artery; LAD = left anterior descending coronary artery.
QRS complex was associated with a discrete epicardial activation sequence. In each run of TdP, the QRS morphology changed in concert with a change in the site of earliest epicardial activation and in the pattern of epicardial spread. The degree of change in QRS morphology followed the degree of change in epicardial activation. If the site of epicardial breakthrough moved to a nearby site, then the QRS morphology changed only slightly (figs. 2E and F). If the earliest site of epicardial activation moved to a considerably different area of the epicardium, then the QRS morphology changed more dramatically (figs. 2F and H). A shift from an apical location to a basal location for the site of earliest epicardial activation caused the QRS polarity in limb lead II to change from negative to positive.

Two to seven distinct sites of epicardial breakthrough were seen during TdP. Nine runs of TdP had two foci of epicardial breakthrough, five had three foci, three had four foci, one run had five foci, and one had seven foci (fig. 3). During the transition from one QRS morphology to another, changes in the epicardial

**Figure 3.** A limb lead II recording of a run of torsades de pointes induced with an eight-beat salvo of rapid ventricular pacing (cycle length 165 msec). The arrow designates the last paced beat. The three strips are continuous. The highly varying QRS morphology and cycle length are manifestations of seven distinct sites of earliest epicardial breakthrough alternating control of epicardial activation during this run of torsades de pointes. Some QRS morphologies are seen repeatedly.
site of breakthrough could be abrupt. Usually, however, the transitional QRS complexes were associated with epicardial maps that demonstrated two separate sites of epicardial breakthrough (figs. 2C and G). During the transition, one dominant breakthrough site gradually yielded to the other (fig. 2). Furthermore, the QRS width of the transition complexes were narrower than nontransition complexes as a result of wave front fusion.

Cycle lengths for each morphologic grouping of complexes within a run of TdP were highly variable, ranging from 118 to 322 msec (mean 186 ± 36 msec). The cycle lengths were similar within a morphologically similar group of QRS complexes. However, cycle length would change after a change in the site of epicardial breakthrough which, in turn, resulted in a dif-

Figure 4. Correlation of isochronous maps of epicardial activation with changing QRS morphology during simulation of torsades de pointes by two widely separated endocardial pacemakers firing at varying rates. Stimuli are delivered to bipolar plunge electrodes secured to the right and left ventricular (RV and LV) endocardium. The format is similar to that of figure 2. (A) The LV pacing site predominates with early epicardial breakthrough occurring high on the anterior LV near the left anterior descending coronary artery (LAD). (E) Control of epicardial activation gradually shifts to the RV pacing site which demonstrates earliest epicardial breakthrough near the RV apex. (I) Epicardial activation is again controlled by the LV pacing site and is nearly the same as the epicardial activation pattern in panel A.
ferent QRS morphology. There was no pattern in the variation in cycle lengths. The QRS complexes with shorter cycle lengths did not necessarily predominate. Some epicardial foci of earliest activation with shorter cycle lengths were superceded by other epicardial foci of earliest activation with longer cycle lengths.

In the two dogs in which it was attempted, TdP was simulated by pacing at varying rates from two widely separated endocardial sites. As in the TdP observed after quinidine administration and acute myocardial ischemia, changes in QRS morphology correlated closely with changes in the site of earliest epicardial activation (fig. 4). All transitional QRS complexes were associated with epicardial maps that showed fusion of epicardial activation as it spread from the two sites of epicardial breakthrough (fig. 4C). The transition QRS complexes during simulated TdP were also narrower than nontransitional complexes, a finding consistent with fusion cycles and shorter activation times.

**Discussion**

Little progress has been made in defining the genesis of TdP. Some investigators have implicated reentry\(^7,25\) as its basic mechanism. Dessertenne\(^12\) favored an automatic mechanism. To resolve the reentry-automaticity controversy, mapping studies with a large number of endocardial, intramyocardial and epicardial electrodes are required. However, mapping with a moderate number of electrodes distributed over the epicardium explains one aspect of the electrophysiology of TdP: how TdP creates the characteristic QRS morphologic changes in the surface ECG for which it is distinctive.

Several mechanisms have been proposed to explain the morphologic features of TdP, but none has been substantiated. Dessertenne\(^12\) believed that the characteristic electrocardiographic findings may occur if two automatic ventricular pacemakers, firing slightly out of phase, alternate control of the ventricles. Smirk and Ng\(^26\) envisioned TdP as an idioventricular focus intermittently subject to progressive ventricular refactoriness, as if spread of activation were encountering a global ventricular Wenckebach phenomenon. Ahronheim\(^27\) suggested that TdP results from a precession of the mean QRS axis. He proposed that during a tachyarrhythmia, if the ventricular polarization cycle is destabilized, the mean QRS vector could gyrate in space.

This study of epicardial activation during TdP does
establish one explanation for the electrocardiographic features of TdP. The QRS morphology of the surface ECG and the sequence of epicardial activation are closely linked: The unique morphologic characteristic of TdP is apparently related to a changing pattern of epicardial breakthrough and epicardial spread (fig. 2). There was no evidence to support a mechanism of a global ventricular refractoriness or global Wenckebach phenomenon. Furthermore, a precession of QRS axis was not seen. Similarly, the change in QRS morphology was not associated with acceleration or deceleration of the epicardial activation wave front arising from a single focus.

The findings that QRS morphology changes in concert with a change in the site of earliest epicardial activation and with a change in the pattern of epicardial spread were verified when TdP was simulated. Simulated TdP was accomplished by pacing simultaneously from two widely separated endocardial sites in two dogs that did not undergo any surgical or pharmacologic interventions. With one pacing wire in the right ventricular endocardium and the other in the left, simultaneous pacing at different and varying rates yielded a QRS that alternated from a right to a left bundle branch block pattern according to which pacing site primarily controlled epicardial activation and the site of earliest epicardial breakthrough (fig. 4). This simulated TdP had the same morphologic characteristics of that in quinidine-intoxicated, infarcted dogs; that is, simulated TdP showed alternating foci of early epicardial breakthrough and changing patterns of epicardial spread of activation as well as narrow transition complexes.

These observations on the electrocardiographic features of TdP as they relate to epicardial activation are founded on a model that, in part, differs from clinical TdP. It is a complex model that incorporates quinidine administration with coronary occlusion and ventricular pacing in the presence of cardiopulmonary bypass. Although TdP certainly occurs clinically during quinidine administration with resultant QT interval prolongation, and has recently been reported during myocardial infarction, it is a spontaneous rhythm. Our model differs from the clinical situation in that burst pacing was necessary to induce TdP in four of five dogs. Furthermore, a critical aspect of our protocol was cardiopulmonary bypass. In our experience, open-chested, acutely infarcted dogs are prone to fluctuation in core temperature, blood pressure and cardiac output. The latter two variables can be particularly unstable during multiple runs of ventricular arrhythmias. By stabilizing temperature and hemodynamic variables with cardiopulmonary bypass, ventricular arrhythmias were much more easily sustained and reproducible (Bardy GH et al.: unpublished observations). The fact that some runs of TdP exceeded 160 seconds may in part be attributed to hemodynamic stability provided by cardiopulmonary bypass.

Given that this model has extenuating aspects to it, it nevertheless yielded 19 tachyarrhythmias that by all known electrocardiographic criteria satisfied the definition of TdP. The QRS morphology characteristically changed in an undulating fashion; the arrhythmia terminated spontaneously, distinguishing it from ventricular fibrillation; and the QT interval was prolonged. While it may be hypothesized that TdP occurs by other mechanisms in other situations, this remains to be shown.

Crucial to understanding TdP is whether reentry or automaticity occurs in the localized region that encompasses the arrhythmogenic tissue. However, in our model, this question is not the key determinant for the unusual electrocardiographic finding that has piqued such interest in this arrhythmia. Whatever mechanism gives rise to the different epicardial activation sequences with their different sites of epicardial breakthrough, the QRS morphology is still determined by spread of activation away from the localized region of arrhythmia origin throughout the remaining ventricular muscle.

In our model, observations in simulated and induced TdP indicate that TdP can be characterized as a ventricular arrhythmia with two or more epicardial breakthrough sites vying for control of epicardial activation. With each change in the earliest site of epicardial activation, a change in QRS morphology can be expected. The narrow transition complexes, or "spindles" that link morphologically distinct QRS complexes, result from fusion of two colliding cycles of epicardial depolarization.

**Acknowledgment**

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**References**

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