Torsades de Pointes: A Review

RADE B. VUKMIR, MD

The electrocardiographic features of a variant, polymorphic ventricular tachycardia were first reported in 1923 by Maunder. The atypical ventricular arrhythmia was termed "transient ventricular fibrillation" by Schwartz in 1949. More recently, cases of refractory ventricular arrhythmias occurring in patients treated with quinidine were reported. This effect was termed "quinidine syncope" by Selzer in 1964 and was attributed to an abnormal ventricular tachycardia. However, the first definitive treatise describing this atypical ventricular tachycardia designated "torsades de pointes," is attributed to Dessertenne in 1966.4

DEFINITION

Polymorphic ventricular tachycardia was described originally as a rapid ventricular rhythm with a typical undulating "twisting about a point" morphology, a prolonged QT interval, and a T-wave that does not return to the isoelectric line" (Figure 1). Later descriptions of torsades de pointes (TDP) focus on 5 to 20 beat paroxysms of ventricular tachycardia characterized by changing heart rate, a polymorphic QRS with progressive modification of amplitude, and polarity of the complexes that vary about an isoelectric baseline (Figure 2). These complexes were described as being refractory to standard therapy. They often terminate spontaneously and frequently recur. The electrocardiographic features of TDP include: (1) multiformal ventricular ectopic complexes that vary symmetrically about an isoelectric axis at a rate of 150 to 300 per minute; (2) commonly, a prolonged QT interval with QT > 60 seconds or QTc > 40 seconds. (Figure 3), (3) an association with ectopy: bradycardia, or high-grade atrioventricular (AV) block, (4) a "long-short" initiation sequence featuring a late premature ventricular complex with a prolonged coupling interval (0.44 to 0.68 seconds) involved in an "R and T" phenomena; (5) a rhythm refractory to conventional therapeutic modalities; and (6) the ability to revert spontaneously or to progress to a more malignant arrhythmia such as nonpolymorphic ventricular tachycardia or fibrillation.4-10

SIGNIFICANCE

Ventricular tachycardia and fibrillation are responsible for 30% to 85% of sudden cardiac death victims. This is significant because TDP is believed to be a transition between these two malignant ventricular arrhythmias.11-12 In fact, TDP has been designated "ventricular fibrillo-flutter" by some authors.13 Wiggers, in a mechanical analysis of ventricular fibrillation, suggested four convulsive stages including involuntary (1 to 2 seconds), convulsive (15 to 40 seconds) with a frequency of 600 to 700 per minute, tremulous (2 to 3 minutes) with a frequency of 600 to 1,000 per minute followed by an atrial phase.14 Koosman, using cinematographic observations, concluded that TDP was analogous to the undulating or preexcitation phase of ventricular fibrillation.15

Incidence is addressed in a small, prospective study examining 15 patients who underwent Holter monitoring for presumed arrhythmia.15 Nonpolymorphic ventricular tachycardia was found in 53% (5 of 15) of patients and associated with a 20% rate of successful resuscitation.15 Polymorphic ventricular tachycardia was also found in an equal distribution 33% (5 of 15) of patients. The larger than expected incidence and higher rate of resuscitation (80%) is noteworthy. Thus, it is important to differentiate polymorphic versus nonpolymorphic ventricular tachycardia in that their pathogenesis, electrophysiology, and response to therapy differ.13,14 TDP has been diagnosed in patients of a wide age range, from the newborn to 80 years.13,16 Predisposition is noted in patients who have a history of ventricular arrhythmia and who experience a recent symptomatic increase in the frequency and complexity of ectopy.13 Symptoms noted by patients include palpitations, dizziness, and syncope followed in some cases by sudden death.13

MECHANISM

TDP has been described as a "maximal vulnerability arrhythmia, where premature stimulation during apical ventricular susceptibility occurs."17 The electrophysiological mechanism for the origin of this arrhythmia was first proposed by Dessertenne as two or more automatic foci competing for control of epicardial depolarization.4 Koosman suggested a mechanism of "asynchronous recovery of excitability" creating various exit sites resulting in macroscopic or microscopic reentry.13,18 Somberg cited "dispersion of refractoriness," occurring with left stellate ganglion stimulation, hypothermia, or myocardial ischemia as the causative factor in the development of TDP.19,20 An interesting study that

From the Division of Emergency Medicine, and the Department of Critical Care Medicine, Presbyterian-University Hospital, Pittsburgh, PA.

Address reprint requests to Dr. Vukmir, Division of Emergency Medicine, University of Pittsburgh School of Medicine, 230 Murray Hall, Suite 500, Pittsburgh, PA 15261.

Manuscript received September 14, 1990; revision accepted December 24, 1990.

Keywords: Torsades de pointes, polymorphic ventricular tachycardia, hypothyroidism

Copyright © 1991 by W.B. Saunders Company

0735-7677/91/0903-0013S5.00/0

250
used a computer-simulated model of arrhythmia generation found that multiple suggested mechanisms are plausible and probably implicated in the generation of TDP. These mechanisms include coincidence of two pathologic foci with differing periods of impulse generation, disturbance of conducting system velocity, a single mobile pathologic focus, AV reentry, and differing repolarization periods of a pathologic ventricular focus with oscillating impulse generation.

Specific electrocardiographic correlates of TDP include bradycardia, dependent triggering of an escape focus of automaticity that features a prolonged action potential. The "long-short" activation sequence occurs when a late premature ventricular contraction encounters an inhomogenous recovery of ventricular repolarization. Thus, the precipitating cycle (short) is followed by the initiating cycle (long) designated, the postectopic pause. This is believed to be the most likely mechanism of initiation as determined by two studies that found this phenomenon in 95% to 100% of TDP cases.

Extrastolic activity has also been cited featuring increases in complexity with summation and fusion of multiple ectopic foci. The timing of extrastolic activity is also implicated with early premature ventricular contractions causing the "R or T" phenomenon and late premature ventricular contractions encountering the U-wave.

The hallmark of TDP, however, is a prolonged QT interval representing the time from ventricular activation (QRS complex) to completed repolarization (T-wave). The electrocardiographic finding of a prolonged QT interval without increased dispersion of repolarization and is believed to be necessary to differentiate TDP from nonmonomorphic ventricular tachycardia. Prolongation of the QT interval is defined as QT > 0.40 to 0.60 seconds. However, the most consistent indicator of QT prolongation is a QT > 0.60 seconds or QTc > 0.45 seconds found in 100% of TDP patients in two studies.

**ETIOLOGY: SPECIFIC CONDITIONS**

TDP can be initiated by numerous conditions and agents (Table I). The Long QT Syndrome (LQTS) is a familial condition originally described in 1957. The familial variant or Jervell and Lange-Nielsen Syndrome is characterized by autosomal recessive transmission, prolonged QT interval (QT > 440 milliseconds), syncope, congenital deafness, T-wave alternans, bradycardia, and abnormal ventricular repolarization. The Romano-Ward Syndrome, with autosomal dominant transmission but no hearing deficit and a nonfamilial idiopathic variant, have also been discussed.

Cardiac disease manifested as myocardial ischemia, myocardial infarction, bradyarrhythmia, myocarditis, and cardiomyopathy has been implicated. In one series, myocardial ischemia has been found in 71% (31 of 25) of patients. Myocardial infarction can be associated with TDP; the risk possibly related to the heterogeneity of repolarization, alternans calcium flux, or imbalance of sympathetic and parasympathetic tone. Other cardiac arrhythmias have been reported in 94% (30 of 32) of TDP patients studied. High-grade AV block has been cited as a causative factor, occurring in as many as 30% (3 of 15) of TDP patients. Another study found that 100% of patients exhibited sinus bradycardia before the onset of TDP.
TABLE 1. Urology of Torsades de Pointes

1. Congestive CHF Prolongation Syndrome
   - Ahluwalia-Matsumoto
   - Romano-Ward
   - Carstairs
   - Myocardial ischemia
   - Myocardial infarction
   - Myocarditis
   - Antitubercular blocks
   - Epinephrine toxicity
   - Hypokalemia
   - Hypomagnesemia
   - Hypocalcemia
   - Hyponatremia
   - Nephrotoxicity
   - Pneumoperitoneum
   - Hypothermia
2. Adrenergic Agents
   - A. Sympathomimetic agents: 
     - Ephedrine
     - Theophylline
     - Nicotine
     - Cocaine
     - Cholinergic agents
     - B. Anticholinergic agents
6. Antiparkinsonian agents
   - A. Antihistaminic agents
   - B. Antidepressants
   - C. Antihypertensive agents
   - D. Truckers
   - E. Immune modulators
3. Antiarrhythmic Agents
   - A. Sodium Channel Blockers
   - B. Calcium channel blockers
   - C. Beta blockers
   - D. Alpha blockers
   - E. Miscellaneous

4. Intravenous inotropic agents

5. slow sodium channel increasing the action potential duration and effective refractory period of the SA and AV nodes. This is a novel role of the adenosine agonist, which has been shown to prolong the QT interval. In patients with chronic heart failure, treatment with adenosine agonists may be beneficial by reducing the risk of arrhythmias.

6. Diltiazem is a calcium channel blocker that slows the rate of spontaneous depolarization (phase 4) by interfering with the slow sodium channel, increasing the action potential duration and effective refractory period of the SA and AV nodes. This is a novel role of the adenosine agonist, which has been shown to prolong the QT interval. In patients with chronic heart failure, treatment with adenosine agonists may be beneficial by reducing the risk of arrhythmias.

7. The therapeutic goal is to decrease the QT interval or repolarization delay due to the dispersion of refractoriness.

8. Mechanical intervention includes the use of an electronic pacemaker to increase heart rate and decrease the QT interval. Intra-atrial pacing produces a ventricular filling and is the preferred pacing mode unless contraindicated by the presence of AV block. Ventricular pacing has proven effective in the suppression of TDP.


Electrolyte abnormalities have been associated with this arrhythmia; although TDP has been described in a study of 21 patients without electrolyte abnormalities, ischemia, or antiarrhythmic therapy. Hypokalemia is found in a number of studies of TDP patients (serum potassium levels of less than 3.7 mEq/L in 62% [20 of 32] and 4.0 mEq/L in 54% [12 of 24] of cases). Hypomagnesemia has also been linked with TDP (magnesium levels of less than 2.2 mg/dL in 62.5% [20 of 32] of TDP patients). However, two studies of TDP patients found no cases that were hypomagnesemic in the onset of the arrhythmia. Neurologic involvement is implicated by left stellate ganglion overactivity resulting in increased dispersion of myocardial repolarization. This involvement is supported by the fact that left stellate ganglionectomy has proven curative in a significant number of cases.

Therapy with pharmacologic agents is the most common etiology of TDP. The cardiovascular effects of psychotropic medications are well documented. The phenothiazines affect action potential duration and amplitude by decreasing the slope of phase 0, prolonging the duration and amplitude of phase 2, and prolonging phase 3 repolarization, resulting in an increased QT interval and U-wave amplitude. Thoridazine is the most commonly involved agent of this class. Tricyclic antidepressants are also implicated because of a quinidine-like effect that results in prolongation of the PR, QRS, and QT interval. Antiarhythmic drugs have demonstrated a significant causal relation in TDP related to their intrinsic ability to prolong the QT interval. A study of 32 patients with TDP found that 88.6% (22 of 26) of cases were being treated with antiarrhythmics. Patients developing TDP have a higher frequency of idiosyncratic, rather than dose-dependent reactions, usually occurring at the initiation of therapy. Patients treated with quinidine often develop TDP at or below therapeutic serum levels.

Analysis of antiarrhythmic agents as the cause of TDP is simplified using the Vaughan-Singh-Williams classification system. Class I agents are sodium (fast) channel blockers that slow conduction velocity by decreasing the maximum rate of depolarization (phase 0) without changing the resting membrane potential (phase 4). TDP is classically associated with type IA agents that prolong the action potential, QRS complex, and QT interval. Quinidine is associated with the highest proarrhythmic potential and is the most common cause of prolonged QT syndrome resulting in the onset of polymorphic ventricular tachycardia. The incidence of quinidine use in patients with TDP has been as high as 40% (4 of 10) in 83.3% (20 of 24) in some series. In addition, quinidine has a significant association with risk factors related to the development of TDP including hypokalemia and high-grade AV block. Quinidine therapy is associated with a 1.3% risk per year of developing TDP. Procainamide, another IA agent, and its active metabolite N-acetylprocainamide (class III) are also strongly associated with the development of TDP. One small study found that 50% (5 of 10) of patients were on procainamide therapy compared with 40% (4 of 10) on quinidine therapy. Disopyramide has also been implicated, although the original description found toxic drug levels, unlike quinidine, or to a lesser extent procainamide in which nontoxic drug levels are more common. There is also an attendant risk when patients are treated with ajmaline, an investigational antiarrhythmic agent. Collectively, the use of type IA antiarrhythmic drugs associated with a prolonged QT interval is the most common predisposing factor to the development of TDP.

Other antiarrhythmic medications have been selectively associated with TDP. Class IB agents slow conduction velocity preferentially in ischemic tissue that has a less negative resting membrane potential, resulting in a decreased action potential duration (APD) and QT interval. The lidocaine congeners, mexiletine, tocainide, and aprindine, have occasionally been associated with TDP. Class IC agents have no effect on action potential duration but lengthen the QRS and QT interval and have not been linked to the development of TDP.

Class II agents are sympathetic antagonists that depress adrenergically stimulated phase 4 depolarization along with
TABLE 1. Pathogenesis of Torsades de Pointes

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Sodium channel blockers</td>
<td>increases action potential duration</td>
</tr>
<tr>
<td>II</td>
<td>Long QT syndrome</td>
<td>pre-existent long QT interval</td>
</tr>
<tr>
<td>III</td>
<td>Antiarrhythmic drugs</td>
<td>decreases repolarization phase 3</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium channel blockers</td>
<td>increases action potential duration</td>
</tr>
</tbody>
</table>

In the long QT syndrome, the QT interval is prolonged due to a defect in the repolarization phase 3 of the action potential. Agents that prolong the QT interval, such as some antiarrhythmic drugs and calcium channel blockers, can induce torsades de pointes. The risk is greatest in the presence of electrolyte disturbances or drugs that potentiate the QT prolongation. The management of torsades de pointes includes identifying and discontinuing the causative agent, correcting electrolyte imbalances, and administering antiarrhythmic agents if necessary. Early recognition and prompt treatment are crucial to prevent cardiac arrest.

Therapy

In the absence of an immediate life-threatening arrhythmia, the primary treatment involves the discontinuation of the causative agent. In cases of a long QT syndrome, electrolyte imbalances and medications that prolong the QT interval should be identified and corrected. For torsades de pointes due to electrolyte abnormalities, intravenous fluids, magnesium, and potassium are used to normalize the electrolyte levels. Antiarrhythmic therapy may be necessary in cases where the arrhythmia is not self-limiting or if there is evidence of hemodynamic instability.

In summary, torsades de pointes is a serious cardiac arrhythmia that requires prompt recognition and appropriate management to prevent potential cardiac arrest. Early intervention is critical to improve outcomes. Further research is needed to develop more effective prophylactic strategies and improve outcomes in patients with torsades de pointes.
Electrolyte abnormalities have been associated with this arrhythmia; although TDP has been described in a study of 21 patients without electrolyte abnormalities, ischemia, or antiarhythmic therapy. Twenty-five Hypokalemia is found in a number of studies of TDP patients. Serum potassium levels of less than 3.7 mEq/L in 62% (20 of 32) and 4.0 mEq/L in 54% (12 of 24) of cases. Twenty-five Hypomagnesemia has also been linked with TDP (magnesium levels of less than 2.2 mg/dL in 62.5% (20 of 32) of TDP patients). Twenty-four However, two studies of TDP patients found no cases that were hypomagnesemic in the onset of the arrhythmia. Twenty-three Neurologic involvement is implicated by left stellate ganglion overactivity resulting in increased dispersion of myocardial repolarization. Twenty-four This involvement is supported by the fact that left stellate ganglionectomy has proven curative in a significant number of cases.

Therapy with pharmacologic agents is the most common etiology of TDP. The cardiovascular effects of psychotropic medications are well-documented. The pharmacokinetic effect action potential duration and amplitude by decreasing the slope of phase 0, prolonging the duration and amplitude of phase 2, and prolonging phase 1 repolarization, resulting in an increased QT interval and U-wave amplitude. Thirty-three Thioridazine is the most commonly involved agent of this class. Thirty-three Tricyclic antidepressants are also implicated because of a quinidine-like effect that results in prolongation of the PR, QRS, and QT interval. Thirty-two Antiarrhythmic drugs have demonstrated a significant causal relation in TDP-related to their intrinsic ability to prolong the QT interval. Thirty-two A study of 32 patients with TDP found that 84.6% (22 of 26) of cases were treated with antiarrhythmics. Thirty-two Patients developing TDP have a higher frequency of idiopathic, rather than dose-dependent reactions, usually occurring at the initiation of therapy. Thirty-two Patients treated with quinidine often develop TDP at or below therapeutic serum levels. Thirty-two Analysis of antiarrhythmic agents as the cause of TDP is simplified using the Vaughan-Williams classification system. Thirty-two Class I agents are sodium (fast) channel blockers that slow conduction velocity by decreasing the maximum rate of depolarization (phase 0) without changing the resting membrane potential (phase 4). Thirty-two TDP is classically associated with type IA agents that prolong the action potential, QRS complex, and QT interval. Quinidine is associated with the highest proarrhythmic potential and is the most common cause of prolonged QT syndrome resulting in the onset of polymorphic ventricular tachycardia. Twenty-three Twenty-two The incidence of quinidine use in patients with TDP has been as high as 40% (4 of 10) to 83.3% (20 of 24) in some series. Twenty-two Twenty-two In addition, quinidine has a significant association with risk factors related to the development of TDP including hypokalemia and high-grade AV block. Twenty-two Quinidine therapy is associated with a 1.5% risk per year of developing TDP. Twenty-two Twenty-two Procainamide, another IA agent, and its active metabolite N-acetylprocainamide (class III) are also strongly associated with the development of TDP. Twenty-two Twenty-two One small study found that 50% (5 of 10) of patients were on procainamide therapy compared with 40% (4 of 10) on quinidine therapy. Twenty-two Twenty-two Twenty-two Disopyramide has also been implicated, although the original description found toxic drug levels, unlike quinidine, or to a lesser extent procainamide in which nontoxic drug levels are more common. Twenty-two There is also an attendant risk when patients are treated with ajmaline, an investigational antiarrhythmic agent. Twenty-two Collectively, the use of type IA antiarhythmic drugs associated with a prolonged QT interval is the most common predisposing factor to the development of TDP. Twenty-two Other antiarhythmic medications have been selectively associated with TDP. Class IB agents slow conduction velocity preferentially in ischemic tissue that has a less negative resting membrane potential, resulting in a decreased action potential duration (AFD) and QT interval. Twenty-two The lidocaine congeners, mexiletine, tocainide, and aprindine, have occasionally been associated with TDP. Twenty-two Class IC agents have no effect on action potential duration but lengthen the QRS and QT interval and have not been linked to the development of TDP. Twenty-two Class II agents are sympathetic antagonists that depress adrenergically stimulated phase 4 depolarization along with