Torsades de Pointes:
A Review

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The electrocardiographic features of a variant, polymorphic ventricular tachycardia were first reported in 1923 by MacWilliam.[1] The atypical ventricular arrhythmia was termed "transient ventricular fibrillation" by Schwartz in 1949.[2] 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.[3] 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[4] (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[3] (Figure 2). These complexes were described as being refractory to standard therapy. They often terminate spontaneously and frequently recur.[5] The electrocardiographic features of TDP include: (1) multiform 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 $\geq$ .60 seconds or QTc $\geq$ .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 .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.[6-10]

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SIGNIFICANCE

Ventricular tachycardia and fibrillation are responsible for 70% to 85% of sudden cardiac death victims.[11] 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.[9] Wiggers, in a mechanical analysis of ventricular fibrillation, suggested four contiguous 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 atonic phase.[13] Kossman, using cinematographic observations, concluded that TDP was analogous to the undulating or preexcitation phase of ventricular fibrillation.[14]

Incidence is addressed in a small, prospective study examining 15 patients that underwent Holter monitoring for presumed arrhythmia.[15] Nonpolymorphic ventricular tachycardia was found in 33% (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 in 33% (5 of 15) of patients.[15] 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.[12,16]

TDP has been diagnosed in patients of a wide age range, from the newborn to 86 years.[17,18] 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.[18] Symptoms noted by patients include palpitations, dizziness, and syncope followed in some cases by sudden death.[16]

MECHANISM

TDP has been described as a "maximal vulnerability arrhythmia, where premature stimulation during peak ventricular susceptibility occurs."[19] The electrophysiologic 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] Kossman suggested a mechanism of "asynchronous recovery of excitability" creating various exit sites resulting in macroscopic or microscopic reentry.[14] Somberg cited "dispersion of refractoriness" occurring with left stellate ganglion stimulation, hypothermia, or myocardial ischemia as the causative factor in the development of TDP.[20,21] An interesting study that

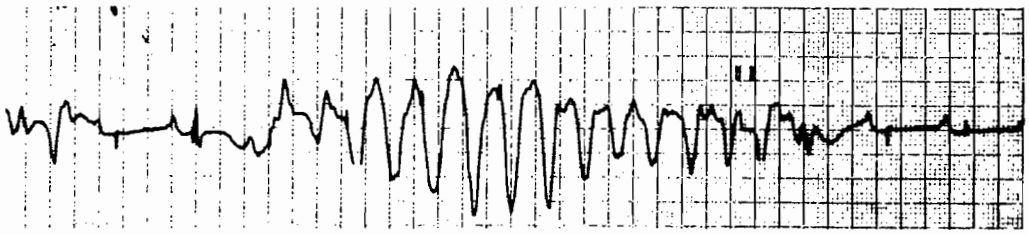

FIGURE 1. "Twisting about a point" morphology.

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.[21]

Specific electrocardiographic correlates of TDP include bradycardia dependent triggering of an escape focus of automaticity that features a prolonged action potential.[22] The "long-short" activation sequence occurs when a late premature ventricular contraction encounters inhomogenous recovery of ventricular repolarization.[12] Thus, the preinitiating 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.[22] Extrasystolic activity has also been cited featuring increases in complexity with summation and fusion of multiple ectopic foci. The timing of extrasystolic activity is also implicated with early premature ventricular contractions causing the "R or T" phenomenon and late premature ventricular contractions encountering the U-wave.[22]

The hallmark of TDP, however, is a prolonged QT interval representing the time from ventricular activation (QRS complex) to completed repolarization (T-wave).[17] The electrocardiographic finding of a prolonged QT interval indicates increased dispersion of repolarization and is believed to be necessary to differentiate TDP from nonpolymorphic ventricular tachycardia.[16] Prolongation of the QT interval is defined as QT $\geq$ .40 to .60 seconds.[22] However, the most consistent indicator of QT prolongation is a QT $\geq$ .60 seconds or QTc $\geq$ .45 seconds found in 100% of TDP patients in two studies.[10,23,24]

ETIOLOGY: SPECIFIC CONDITIONS

TDP can be initiated by numerous conditions and agents (Table 1). The Long QT Syndrome (LQTS) is a familial condition originally described in 1957.[30] 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.[31] The Romano-Ward Syndrome, with autosomal dominant transmission but no hearing deficit and a nonfamilial idiopathic variant, have also been discussed.[31]

Cardiac disease manifested as myocardial ischemia, myocardial infarction, bradyarrhythmia, myocarditis, and cardiomyopathy has been implicated.[32] In one series, myocardial ischemia has been found in 97% (31 of 32) of patients.[10] Myocardial infarction can be associated with TDP; the risk possibly related to the heterogenicity of repolarization, alteration in calcium flux, or imbalance of sympathetic and parasympathetic tone.[20] Other cardiac arrhythmias have been reported in 94% (30 of 32) of TDP patients studied.[10] High-grade AV block has been cited as a causative factor, occurring in as many as 20% (3 of 15) of TDP patients.[15] Another study found that 100% of patients exhibited sinus bradycardia before the onset of TDP.[24]

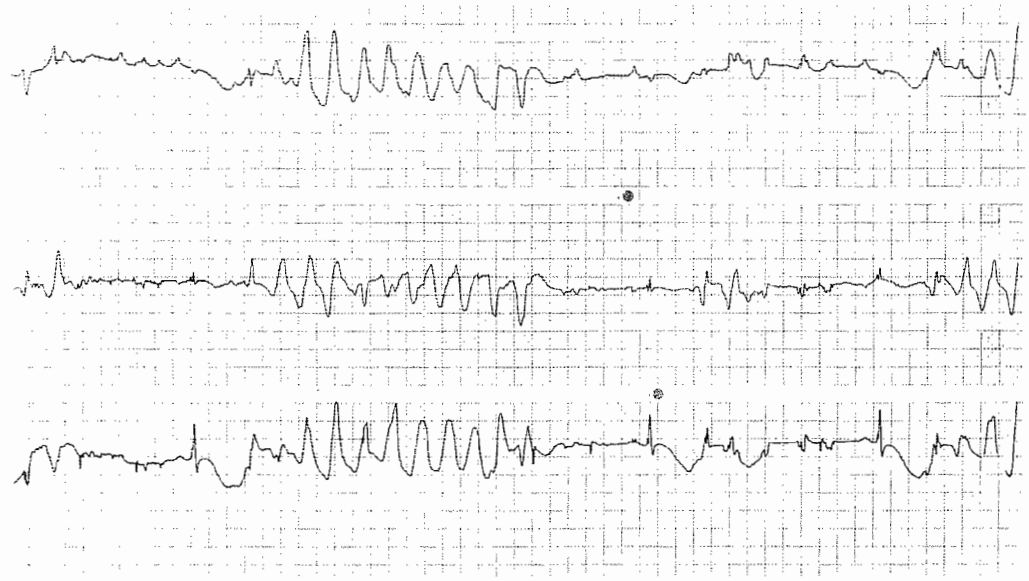

FIGURE 2. Polymorphic ventricular tachycardia.

TABLE 1. Etiology of Torsades de Pointes

1. Congenital QT Prolongation Syndromes
   - Jervell and Lang-Nielson
   - Romano-Ward
2. Cardiac
   - Myocardial Ischemia
   - Myocardial Infarction
   - Myocarditis
   - Bradycardia
   - Atrioventricular Block
3. Electrolyte Abnormalities
   - Hypokalemia
   - Hypomagnesemia
   - Hypocalcemia
   - Liquid Protein Diet
4. Neurologic
   - Subarachnoid Hemorrhage
   - Cerebrovascular Accident
   - Pneumoencephalography
5. Environmental/Toxin
   - Hypothermia
   - Arsenic
   - Organophosphate Insecticides
6. Pharmacologic Agents
   - A. Psychotropic agents:
     - Phenothiazines
     - Thioridazine
     - Trifluroperazine
     - Chloropromazine
   - B. Antidepressants
     - Amitriptyline
     - Imipramine
     - Maprotiline
   - C. Antiarrhythmic Agents
     - I. Sodium (Fast Channel) Antagonists
       - a. Quinidine
         - Procainamide
         - Disopyramide
         - *Ajmaline
       - b. Lidocaine
         - Mexilitene
         - Tocainide
         - *Aprinide
       - c. Encainide
     - II. Sympathetic Antagonists
       - a. Propranolol
     - III. Antifibrillatory Agents
       - a. Amiodarone
       - b. N-Acetyl Procainamide
       - *c. Sotalol
     - IV. Calcium (Slow Channel) Antagonists
       - a. Lidoflazine
       - *b. Bepridil
       - c. Nifedipine
     - V. Anion Antagonists
       - a. None
   - D. Vasodilators
     - *Prenylamine
     - *Fenoxidil
   - E. Miscellaneous
     - Diuretics
     - Corticosteroids
     - Atropine
     - Isoproterenol

* Investigational in the USA[8,12,25,26,27,28,29]

slowing sinoatrial (SA) and atrioventricular (AV) node conduction.[29] Propranolol is the only β-blocker implicated in the development of TDP. Class III agents exhibit antifibrillatory activity by homogenously prolonging the APD, thereby increasing the effective refractory period (ERP).[26] Amiodarone use has been implicated up to 5 weeks after therapy because of a prolonged half life.[17] Sotalol, a nonselective β-blocking drug with class II and III activity, has a significant association with TDP.[20] Class IV consists of calcium channel-blocking agents that slow 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.[29] Two investigational vasodilators have been associated with TDP, lidoflazine and bepridil, that prolong the QT interval.[25] Nifedipine is the only commonly-used calcium channel antagonist cited as a cause of TDP.[25] Finally, class V agents that act as anion antagonists have not been related to the development of TDP.[28]

THERAPY

Cornerstones of TDP management include prevention, correction of underlying causes, use of pharmacologic agents to shorten the ventricular refractory period, and avoidance of antiarrhythmic drugs that may exacerbate the arrhythmia.[14] The therapeutic goal is to decrease the QT interval or repolarization delay due to the dispersion of refractoriness.[19]

Mechanical intervention includes the use of an electronic pacemaker to increase heart rate and to decrease the QT interval.[25] Atrial pacing preserves the atrial contribution to ventricular filling and is the preferred pacing mode unless contraindicated by the presence of AV block.[29] Ventricular pacing has proven effective in the suppression of TDP.[24,10] Overdrive pacing should be instituted at a rate of up to 120 per minute until the QT interval is normalized.[40,25] Cardiac pacing is safe and effective but requires skill, specialized equipment, and a considerable delay until the institution of therapy.[7] Cardioversion is described as a last resort effort for persistent TDP because the rhythm is paroxysmal and will commonly recur following cardioversion. Progression to ventricular fibrillation may occur.[8] Studies have demonstrated clinical efficacy in 60% to 100% of cases; however, all patients reverted back to TDP.[10,24]

Pharmacologic modalities include vasopressor agents, antiarrhythmic drugs, and electrolyte repletion. Isoproterenol, a sympathomimetic amine with β-adrenergic activity, accelerates AV conduction and decreases the QT interval by reducing temporal dispersion of repolarization.[5] Isoproterenol has proven to be effective for TDP in both animal and human studies.[7,24] Relative contraindications to the use of isoproterenol include angina, myocardial infarction, and hypertension; it can also be deleterious in monomorphic ventricular tachycardia.[33] Thus, isoproterenol is recommended for use in TDP only as an interim agent, until cardiac pacing can be implemented. Atropine has been suggested as effective therapy via its action to inhibit the vagal stimulus to the myocardium and increase AV nodal conduction.[33] Four of 10 TDP patients treated with atropine had a beneficial effect.[24]

Consideration of antiarrhythmic agents is based on the premise that class IA drugs could further exacerbate the development of TDP.[14] In general, type Ia drugs should be avoided, especially in patients who are on antiarrhythmic agents when they develop TDP. In eight patients with TDP who were not on antiarrhythmic agents, procainamide or quinidine caused no change in 90% of patients, but 10% progressed to ventricular tachycardia.[23] Thus, use of class IA drugs for TDP is contraindicated.

Lidocaine is a class IB antiarrhythmic that reduces temporal dispersion of refractoriness, decreasing QT, QTc, action potential duration, and effective refractory period duration.[7] Lidocaine usually causes no change in TDP or

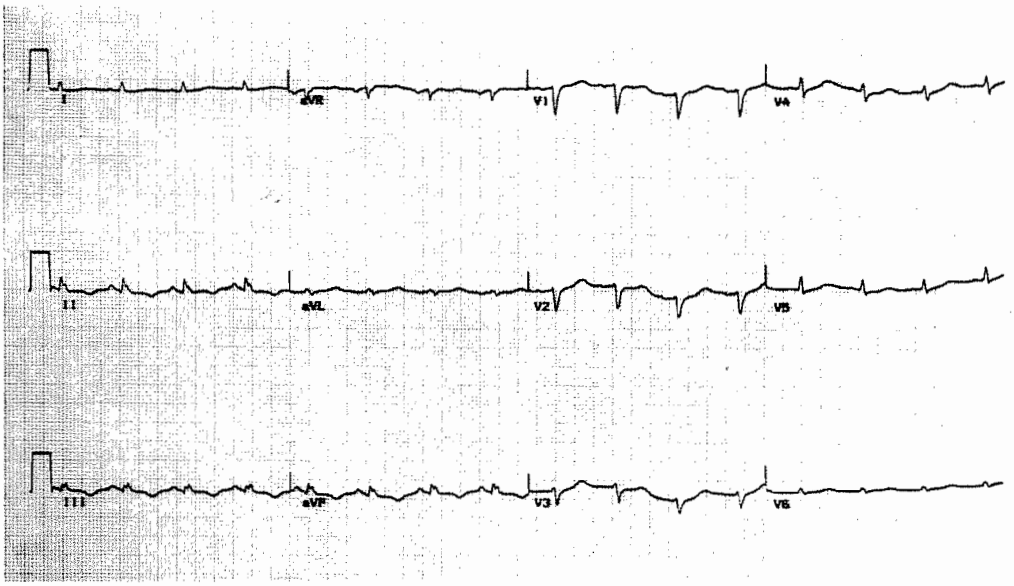

FIGURE 3. Prolonged QT interval.

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.[20,23] 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).[10,18,22] Hypomagnesmia has also been linked with TDP (magnesium levels of less than 2.2 mg/dL in 62.5% [20 of 32] of TDP patients).[10] However, two studies of TDP patients found no cases that were hypomagnesemic at the onset of the arrhythmia.[5,33] Neurologic involvement is implicated by left stellate ganglion overactivity resulting in increased dispersion of myocardial repolarization.[34] This involvement is supported by the fact that left stellate ganglionectomy has proven curative in a significant number of cases.[34]

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.[35] Thioridazine is the most commonly involved agent of this class.[35] Tricyclic antidepressants are also implicated because of a quinidine-like effect that results in prolongation of the PR, QRS, and QT interval.[36] Antiarrhythmic drugs have demonstrated a significant causal relation in TDP related to their intrinsic ability to prolong the QT interval.[20] A study of 32 patients with TDP found that 84.6% (22 of 26) of cases were being treated with antiarrhythmics.[10] Patients developing TDP have a higher frequency of idiosyncratic, rather than dose-dependent reactions, usually occurring at the initiation of therapy.[22,24] Patients treated with quinidine often develop TDP at or below therapeutic serum levels.[22]

Analysis of antiarrhythmic agents as the cause of TDP is simplified using the Vaughan-Singh-Williams classification system.[28] 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).[29] 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.[20,22] 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.[22,24] In addition, quinidine has a significant association with risk factors related to the development of TDP including hypokalemia and high-grade AV block.[22,37] Quinidine therapy is associated with a 1.5% risk per year of developing TDP.[18] Procainamide, another IA agent, and its active metabolite N-acetyl-procainamide (class III) are also strongly associated with the development of TDP.[17,20] One small study found that 50% (5 of 10) of patients were on procainamide therapy compared with 40% (4 of 10) on quinidine therapy.[20,24,38] 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.[38] There is also an attendant risk when patients are treated with ajmaline, an investigational antiarrhythmic agent.[25] 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.[29] The lidocaine cogeners, mexilitene, tocainide, and aprinide, have occasionally been associated with TDP.[28] 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.[29]

Class II agents are sympathetic antagonists that depress adrenergically stimulated phase 4 depolarization along with

may have an initial beneficial effect that reverts to TDP in all cases.[10] Thus lidocaine has no proven benefit. Because it can increase the disparity between ischemic and normal tissue, it cannot be recommended as therapy for TDP. Phenytoin, another IB agent used for arrhythmia control of tricyclic antidepressant and digoxin overdose, restores normal membrane excitability and automaticity by decreasing the effective refractory period and by increasing AV conduction.[41,42] Phenytoin has been effective in treating of TDP in several case reports.[7,8] Bretylium is a Class III agent that helps to minimize the disparity of action potential duration caused by quinidine-like drugs.[25] Its efficacy for TDP is similar to lidocaine, although a single study suggests that bretylium is the superior agent in TDP therapy.[10,43]

Electrolyte repletion therapy has focused on magnesium infusion reported to be efficacious in TDP therapy.[34,44] Hypokalemia is associated with TDP to a greater extent than is hypomagnesemia.[10,22] The presumed mechanisms of action include restoration of intracellular potassium by affecting the Na,K-ATPase system, blocking slow calcium channels, and normalizing repolarization abnormalities.[5] Magnesium acts as a cofactor in the Na,K-ATPase system, facilitating potassium influx into the cell, stabilizing the membrane potential, and correcting the dispersed repolarization process without shortening the QT interval.[33] In one 12-patient study 2 to 4 g of intramuscular magnesium resulted in a 75% response rate within 5 minutes and 100% response by 15 minutes.[33] Another report suggested a magnesium dose of 16 mEq over one hour followed by 1 mEg/kg over 24 hours and 0.5 mEq/kg for 3 days or until the QT interval is less than 0.50 seconds.[33,44] Side effects occurring with rapid infusion include hypotension.[3] Magnesium is easily administered with less risk than Isoproterenol infusion for TDP.

In summary, therapy for TDP includes avoidance of offending agents, correction of magnesium or potassium deficiency, administration of isoproterenol, bretylium, or phenytoin followed by institution of cardiac pacing.

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