Cardiovascular Drugs and Therapy 1991; 5:203–212

Electrophysiologic Mechanisms Involved in the Development of Torsades de Pointes

Silvia G. Priori, Carlo Napolitano, Peter J. Schwartz

Unita' di Studio delle Aritmie, Centro di Fisiologia Clinica e Ipertensione, Istituto di Clinica Medica II, Universita' degli Studi di Milano, Milano, Italy

Summary. ***Torsades de pointes*** **(TDP) is a polymorphic ventricular tachycardia with a peculiar electrocardiographic pattern of continuously changing morphology of the QRS complex twisting around an imaginary baseline. The clinical setting under which TDP develops covers many clinico-pathologic conditions, including the long QT syndrome (LQTS). In the present review, we analyze the evolution of the hypotheses for the mechanisms underlying TDP and we discuss some of the experimental models used and their related clinico-pathologic counterparts. Together with the hypothesis that TDP represents a form of reentrant arrhythmia, recent evidence has suggested the possibility that triggered activity may indeed be responsible for TDP. Data collected in vitro are presented that demonstrate a role for catecholamines in the development of afterpotentials in ventricular tissue. Whether adrenergic-mediated afterdepolarizations are the mechanism responsible for TDP in the clinical setting of LQTS has not yet been proven and remains an important area of investigation.**

Cardiovasc Drugs Ther 1991; 5:203–212

Key Words. **torsades de pointes, long QT syndrome, triggered activity, stellate ganglion**

Torsades de pointes [1] is a polymorphic ventricular tachycardia with a peculiar electrocardiographic pattern of continuously changing morphology of the QRS complex twisting around an imaginary baseline (Figure 1). An additional requirement for a ventricular tachycardia to be defined as *torsades de pointes* is the accompanying prolongation of the QT and QTU interval that often precedes the development of the tachycardia. The clinical setting under which *torsades de pointes* develop includes many clinico-pathologic conditions that share apparently few or no common features (Table 1).

Given such a variety of circumstances under which *torsades* have been described, several additions have been made to the definition of a *torsade*. Brugada [2] suggested that the diagnosis requires the initiation of tachycardia by a late extrasystole. Surawicz [3] has proposed that the arrhythmia has to be suppressible by an increase in heart rate. Finally, Jackman et al. [4] have proposed that, even in the absence of the twisting morphology of the QRS, a tachycardia associated to T and U waves abnormalities could still be called *torsades de pointes*. In spite of such a diversity of opinion, the definition of *torsades* has not simply merged into that of polymorphic ventricular tachycardias, because the arrhythmia still holds its separate profile compared to other forms of tachycardia; this is largely due to the fact that it requires a specific clinical approach and it responds to treatments that are different from those effective with the more common types of ventricular tachycardia.

The difficulties in establishing the prevailing criteria to define a *torsade* stem from the uncertainty on the very mechanisms underlying the development of *torsades* and the variety of models used as experimental preparations in the attempt to mimic the clinical form of *torsades*. In this brief overview, we will analyze the evolution of the hypotheses for the mechanisms underlying *torsades*, and we will discuss some of the experimental models used and their related clinico-pathologic counterparts.

Searching for a Hypothesis

Since 1966, when the original work by Dessertenne [1] called attention to *torsades de pointes* as a peculiar type of ventricular tachycardia, the search for the understanding of the cause for the twisting morphology of the QRS has flourished. In spite of several efforts, almost three decades of work from many groups have not yet proven a universally accepted mechanism that could account for the various aspects of the arrhythmia. However, many contributions have im-

Address for correspondence and reprint requests: Peter J. Schwartz, M.D., Istituto di Clinica Medica II—Pad. Sacco, Via F. Sforza, 35, 20122 Milano, Italy.

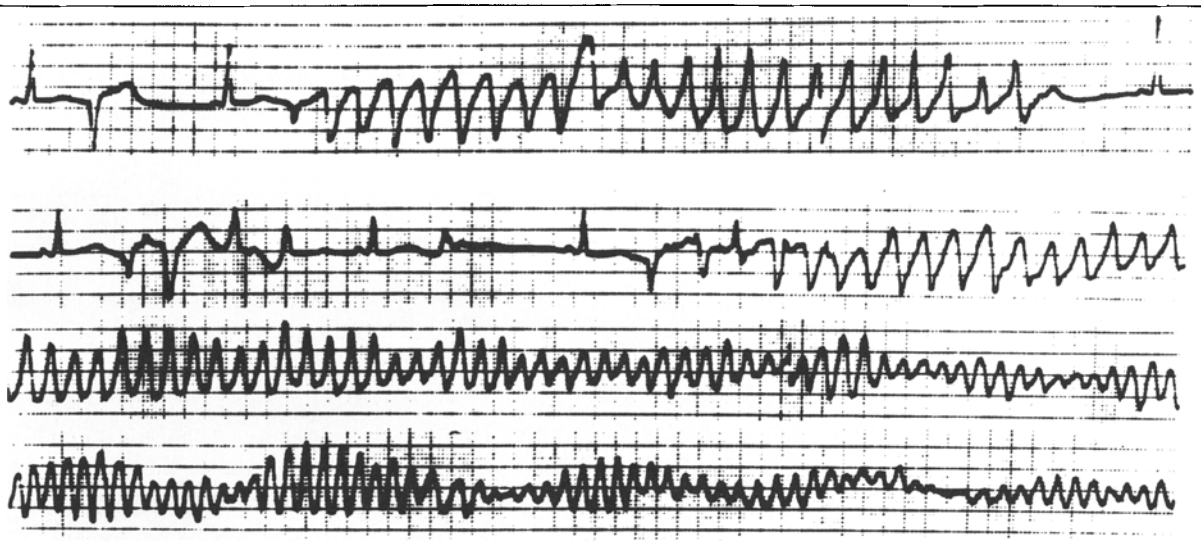

Fig. 1. *Example of* torsades de pointes *in a patient receiving quinidine. (From: Coumel P, Leclercq JF, Dessertenne F. Torsades de pointes. In: Josephson M, Wellens HJJ, eds.* Tachycardias: mechanisms, diagnosis, treatment. *Philadelphia: Lea & Febiger 1984;325–351 with permission of the Authors).*

Table 1. *Clinical conditions associated with repolarization abnormalities and* torsades de pointes

Congenital forms
Jervel-Lange-Nielsen syndrome
Romano-Ward syndrome
Drugs and chemicals
Antiarrhythmic agents
Tricyclic antidepressants
Phenothiazines
Organophosphates compounds
Electrolyte disturbances
Hypokalemia
Hypocalcemia
Hypomagnesemia
Nutritional deficits
Anorexia nervosa
Liquid protein diets
Bradyarrhythmias
Complete AV block
Sinus nodal dysfunction
Cerebrovascular accidents

proved our understanding of the several forms of *torsades*, and they have shaped the hypothesis that more than one mechanism can account, under different circumstances, for the development of *torsades*.

"La tachycardie ventriculaire a deux foyers opposes variables"

The first hypothesis was actually supported by Dessertenne [1], who suggested that two automatic foci firing from opposing sites of the heart were competing for excitation of the ventricle, thus accounting for the changing morphology of the QRS. This simple hypothesis, although appealing, was at that time not supported by experimental evidence and was therefore rapidly dismissed. After these several years, we are now in a time in which, under the light of a possible involvement of triggered activity (see below) in the genesis of *torsades*, we could look back and acknowledge new value to this first hypothesis.

The dispersion of refractoriness

Han and Moe showed that a uniform recovery of excitability in the myocardium is very critical to the maintenance of normal impulse initiation and conduction. When duration of the refractory period is not homogenous throughout the ventricle, the ventricular fibrillation threshold (an index of electrical stability) decreases. This suggests that propagation of the excitation under these conditions is very unstable and can easily degenerate into severe ventricular arrhythmias. The likely mechanism for arrhythmias depending on dispersion of refractoriness is the development of reentrant circuits that are favored by the development of unidirectional block in the areas of prolonged refractoriness [5].

Dispersion of refractoriness has been proposed as one of the possible arrhythmogenic mechanisms underlying *torsades de pointes* [3]. This hypothesis suggests that the prolongation of repolarization reflected in the QT and QTU interval lengthening that preceeds *torsades* is not uniform throughout the ventricle, thus leading to a higher vulnerability of the heart to ventricular tachycardia. Evidence of dispersion of repolarization has indeed been obtained in patients with a long QT interval and a history of *torsades de pointes* [6] by the use of monophasic action potential recording. Subjects with a normal QT interval and no

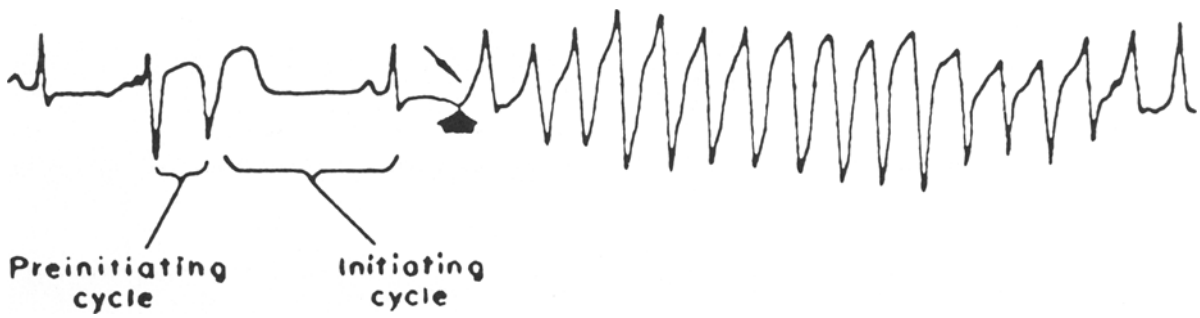

Fig. 2. *Electrocardiogram of a typical paroxysm of quinidine-induced* torsades de pointes *demonstrating the typical cycle length changes just before an episode. The tachycardia starts (light arrow) after the apex of the T wave (heavy arrow). In the vast majority of instances of quinidine-induced* torsades de pointes, *the "initiating cycle" is markedly prolonged and is longer than the "preinitiating" cycle. From Roden et al. [11] with permission from the American College of Cardiology.*

history of *torsades* appear to have a much more uniform duration of action potential [6,7]. The presence of a non-uniform duration of cardiac repolarization in subjects with *torsades* is undoubtedly a strong argument in favor of the hypothesis of dispersion of refractoriness in the genesis of *torsades*. However, the same mechanism has been also proposed for other forms of ventricular arrhythmias, such as those developing in the course of acute ischemia; therefore, this hypothesis does not provide an explanation that accounts for the unique characteristics of *torsades de pointes*.

The short-long-short sequence and afterdepolarizations

Electrocardiographic evaluation in the initiating pattern of an arrhythmic episode is an apparently simple, yet very valuable, approach to the understanding of arrhythmias and provides the advantage of allowing comparison between clinical and experimentally induced *torsades*. This approach can give insights on the extent to which an experimental preparation is pertinent to the clinical setting, as well as enlighten new hypotheses to be tested in the experimental laboratory. The initial observation in 1983 by Kay et al. [8] of the dependence of *torsades* on a typical pattern of onset opened the way to several reports [9–11] that confirmed and extended their initial finding. Here is how Kay et al. described their observation: "A premature ventricular beat . . . was followed by a pause and a subsequent supraventricular beat. Then a premature ventricular beat occurred . . . at a relatively short cycle length and precipitated the *torsades de pointes*." Central to this description is the focus on a long-short initiating sequence. Roden et al. [11] confirmed and further characterized this pattern of initiation for *torsades* by describing that the cardiac cycle immediately preceding the last sinus beat was abnormally prolonged (being often a compensatory pause following a ventricular beat) (Figure 2). The last sinus beat preceding the development of *torsades* had a markedly prolonged QT interval, and the first beat of the ventricular tachycardia often impinged on the terminal portion of the repolarization (R on T phenomenon).

The most remarkable aspect of these observations is the presence of a pause that precedes the prolongation in the following beat. This characteristic pattern of initiation points to a "pause-dependent" or "bradycardia-dependent" mechanism for *torsades*, and therefore to the most classic bradycardia-dependent arrhythmogenic mechanism, the early afterdepolarizations (EADs).

The definition of EADs as depolarizations that interrupt phase 3 of the action potential is fairly recent [12] and, to a certain extent, was preceded by the hypothesis that secondary depolarizations may lead to the genesis of the U wave. When Lepeschkin [13,14] recorded, with the use of monophasic action potentials (MAP), his "afterpotentials" and originally proposed the possibility that these deflections interrupting phase 3 of repolarization could be a likely mechanism for the development of U wave, the definition of EAD had not been created. His theory was vigorously contrasted and then dismissed upon the evidence that intracellular recordings obtained simultaneously to monophasic action potentials [15] failed to confirm the electrical nature of the observed afterdepolarizations as opposed to motion artifacts.

Recently, the use of monophasic action potentials has generated a new surge of interest, mainly related to the availability of a new recording technique developed by Franz [16] that allows more prolonged and stable recordings.

The common interesting observations of several recent studies using the monophasic action potential technique has been the finding of simultaneous development of afterdepolarizations on the monophasic ac-

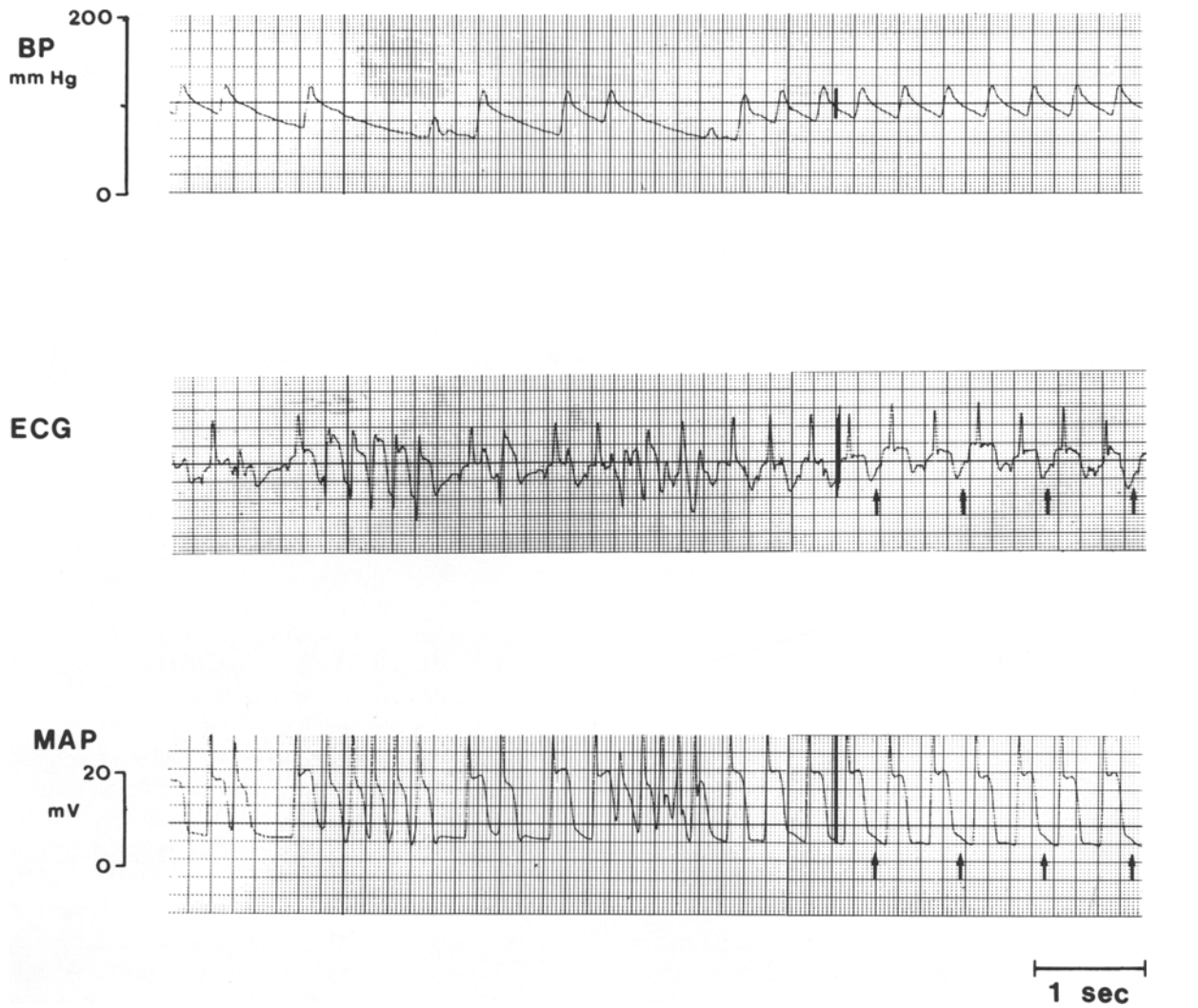

Fig. 3. *Simultaneous recordings of blood pressure (BP, mmHg, top trace), electrocardiograms (ECG, middle trace), and monophasic action potential (MAP, mV, lower trace) a few seconds after reperfusion when arrhythmias develop. Note the presence of early afterdepolarization (EAD) in the lower trace during the sinus beats that interrupt ventricular tachycardia. When arrhythmias terminate, an intermittent 2:1 conduction of EAD is present (arrows, lower trace) and alternans of the T wave appears on the ECG (arrows, middle trace).*

tion potential recordings and of alterations of the TU interval on the surface ECG [4,17–20] (Figure 3). Although the same arguments of concerns for the artifactual recordings that were objected to by Lepeschkin are still [15] raised as a limitation of the validity of monophasic action potential recording, increasing caution in the assessment of stability of the recordings, as well as simultaneous recording of intraventricular pressure [18,21] or combined use of endocavitary as well as surface monophasic action potential catheters [19], has probably increased the reliability of the recording and the ability to distinguish between motion artifacts and electrical events. Therefore, there has been recently an increased consensus for the role of EADs in the genesis of the U waves on the ECG and the onset of triggered arrhythmias. Additionally, since triggered activity is a form of focal activity, the original proposal by Dessertenne [1] of two separate foci competing for activation of the myocardium and responsible for the changing morphology of the QRS in *torsades* has acquired a new interest as a potential explanation for the peculiar morphology of this arrhythmia.

Several aspects seem to fit in the EAD hypothesis; however, some concerns could still be raised. For example, EAD development has generally been reported during markedly slow heart rates that are not always present in the clinical setting of *torsades*.

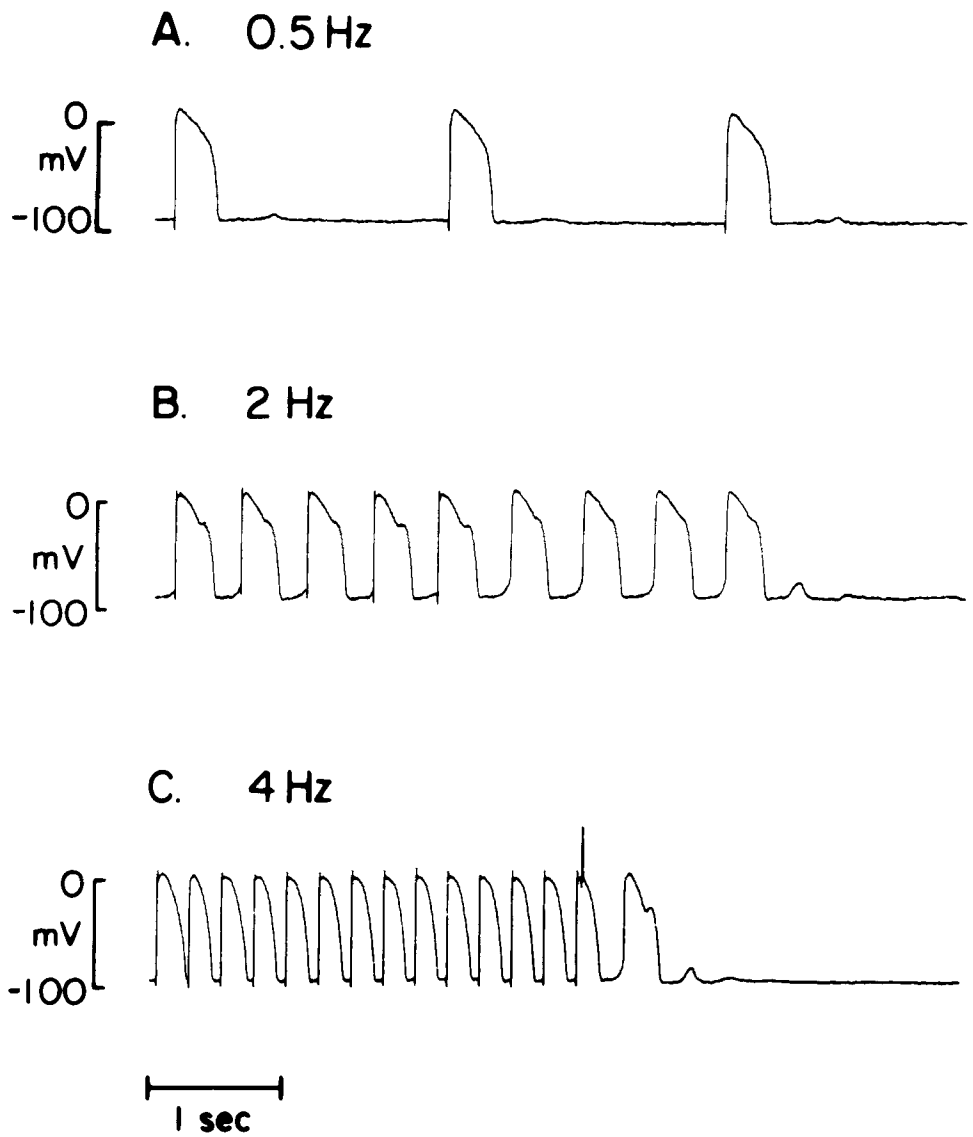

Fig. 4. *Intracellular microelectrode recording in isolated adult canine myocytes exposed to isoproterenol 10^{-6} M. A: Pacing at 0.5 Hz elicits the development of DADs. B: The first five beats are paced at 2 Hz, and the following beats consist of a run of triggered activity that terminates with a subthreshold DAD. Note that EADs develop simultaneously as notches on phase 3 of the action potential. C: Pacing at 4 Hz induces a triggered beat (last of the sequence) that is interrupted by a EAD on phase 3 and is followed by a DAD. Data are taken from Priori and Corr [24].*

Damiano and Rosen [22] showed that the rate at which EADs occurred was close to 60 beats/min; this evidence has been considered by other authors as a deterrent to the hypothesis. However, Cranefield et al., in their review [23], supported the role of EADs in the genesis of *torsades* and reported their unpublished observations and a personal communication by Brian Hoffman that would support the possibility that EADs induced in the presence of catecholamines can also occur at much faster heart rates. Recently, Priori and Corr [24,25] demonstrated that EADs induced by isoproterenol in isolated myocytes still occur at a heart rate above 200 beats/min (see Figure 4), thus not only supporting the idea that adrenergic-EADs develop at faster rates, but also suggesting that maintenance of a ventricular tachycardia, beside its initiation, can still be mediated by EADs induced by isoproterenol.

Since EADs are likely to arise in only a few areas of the myocardium, their development can locally pro-

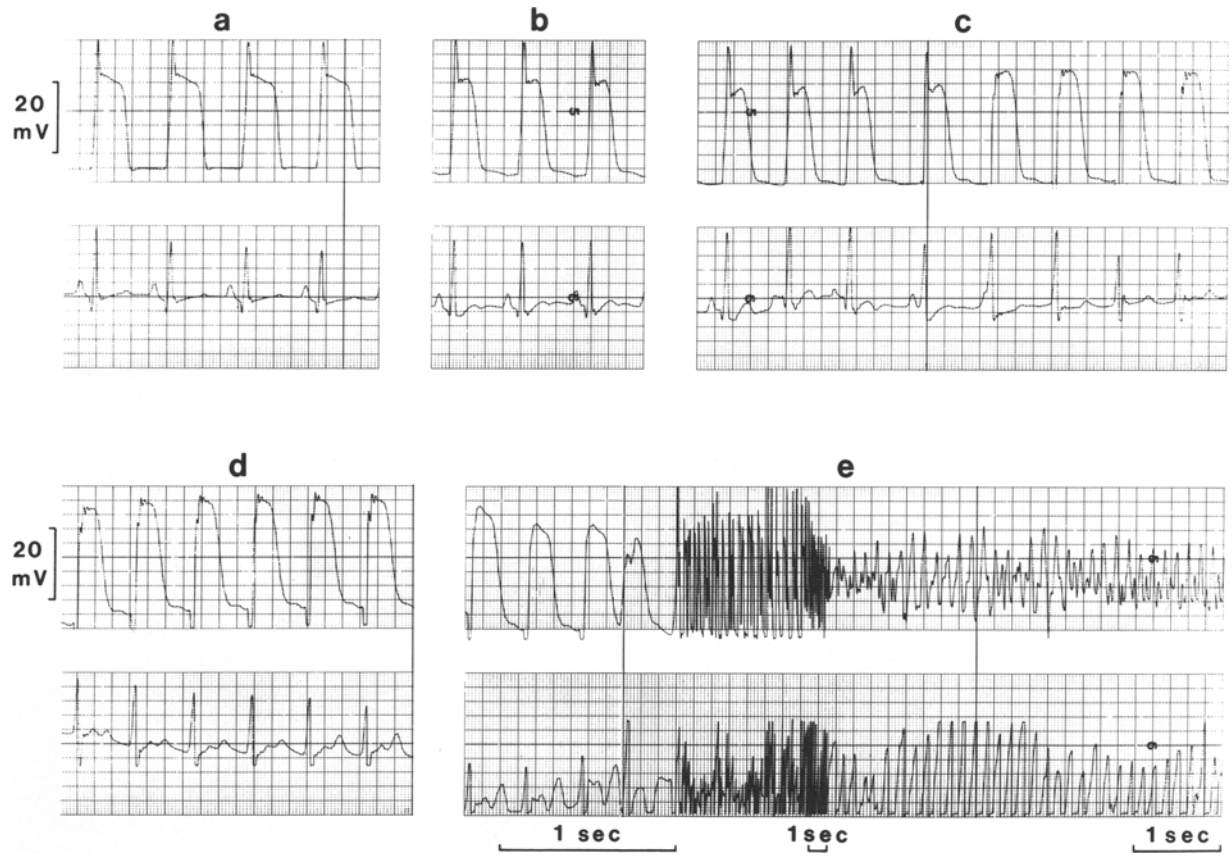

Fig. 5. *Recordings of ventricular fibrillation induced by administration of digitalis plus calcium. Top trace: monophasic action potentials. Bottom trace: electrocardiogram. a: control recording; b: injection of Ca^{2+} digitalis induces a shortening of action potential duration and the appearance of delayed afterdepolarizations. A few seconds later, a junctional rhythm (c) appeared and a progressive increase in amplitude of T wave (d) is observed on surface ECG. As T-wave changes become prominent (e), a premature beat occurs and triggers a run of ventricular tachycardia that rapidly degenerates into ventricular fibrillation.*

long the action potential duration and explain the discrepancies in monophasic action potential duration recorded in patients with prolonged QTU interval in history of *torsades de pointes*. Development of EADs independent from triggered activity can therefore still be arrhythmogenic by creating dispersion of refractoriness and favoring reentrant arrhythmias (see previous section). Under this point of view, the hypothesis of the role of a dishomogeneous repolarization and that of afterdepolarizations would merge into a unique event that could account for the development of *torsades*.

Brugada and Wellens [26] suggested that when EADs develop in one cell, they create a discrepancy in action potential duration among adjacent cells. This event can lead to electrotonic propagation of current that could reexcite cells that have terminated their refractory period acting as an injury currents during ischemia [27]. They called this potentially arrhythmogenic mechanism *prolonged repolarization-dependent excitation*.

A more complex role for afterdepolarizations: "Pause-dependent and adrenergic-dependent long QT syndromes (LQTS)"

It is well established that some repolarization abnormalities preceding the development of *torsades* in LQTS patients, such as alternation of the T wave [28], depend on the presence of catecholamines. On this basis, Jackman and colleagues [29] proposed that delayed afterdepolarization (DADs), as opposed to EADs, are the triggering mechanism for *torsades* in the setting of augmented sympathetic activity. However, beta-adrenergic stimulation has been associated with the development of both EADs [30,24] and DADs. DADs are defined as afterpotentials that arise after the termination of an action potential (diastolic phase) and occur, therefore, later than EADs in the cardiac cycle. Afterdepolarizations dependent on beta-adrenergic stimulation in ventricular tissue have been described in isolated myocytes either during normoxia, as well as in hypoxic conditions, at concentrations of the beta-adrenergic agonist ranging from 10^{-9}

M to 10^{-7} M [24,25]. In vivo, DADs have been induced by activation of the left stellate ganglion [18], and they very much resemble DADs induced by digitalis administration in the same animal model.

DADs recorded in vivo by the use of monophasic action potential recordings are associated with the development of alterations of the repolarization, as demonstrated by changes in the T wave synchronous with DAD appearance (Figure 5).

Jackman et al. [29] have made the suggestion that two different diseases exist in which *torsades* develop following alteration of the QTU interval. They described a "pause-dependent LQTS" that includes most of the causes of *torsades* that we listed in Table 1, such as drug-induced LQTS, electrolyte abnormalities, altered nutritional states, and severe bradyarrhythmias, and suggested that this form is more likely mediated by EADs. The other is defined as *adrenergic-dependent LQTS*, and it mainly includes the familial forms of LQTS (both Jervell-Lange-Nielsen and Romano-Ward) and some cerebrovascular accidents. An intermediate group with characteristics of both is also included in their classification, but it remains less well identified. These two forms of LQTS are distinguished based upon the role of catecholamines in their initiation and the type of afterdepolarizations that are more likely to be responsible for the genesis of *torsades de pointes*.

This approach accounts well for some differences of the two forms of LQTS. For example, *torsades* developing in the bradycardia-dependent LQTS are suppressed by atrial pacing, while efficacy of pacing in the idiopathic LQTS is less consistent. Most of the patients presenting with quinidine intoxication have abnormalities in the QTU interval that are almost invariably enhanced by pauses, thus fitting well the suggested dependence of repolarization changes on EADs. On the other hand, in the idiopathic LQTS, where adrenergic activation is the major triggering event for arrhythmias, the behavior of heart rate is less consistent and will fit better with the hypothesis of a role for DADs. However, recording of monophasic action potentials in patients with the idiopathic LQTS have also suggested the presence of EADs in this patient population.

Jackman et al. have, in fact, recently [4] added to their original hypothesis [29], suggesting that while EADs are still the likely mechanism for *torsades* in the pause-dependent LQTS, both types of afterdepolarizations, as opposed to DADs only, are probably involved in the genesis of *torsades* in the idiopathic LQTS.

The implication of afterdepolarizations in the development of torsades de pointes supports the hypothesis by Dessertenne on the origin of their morphology [1].

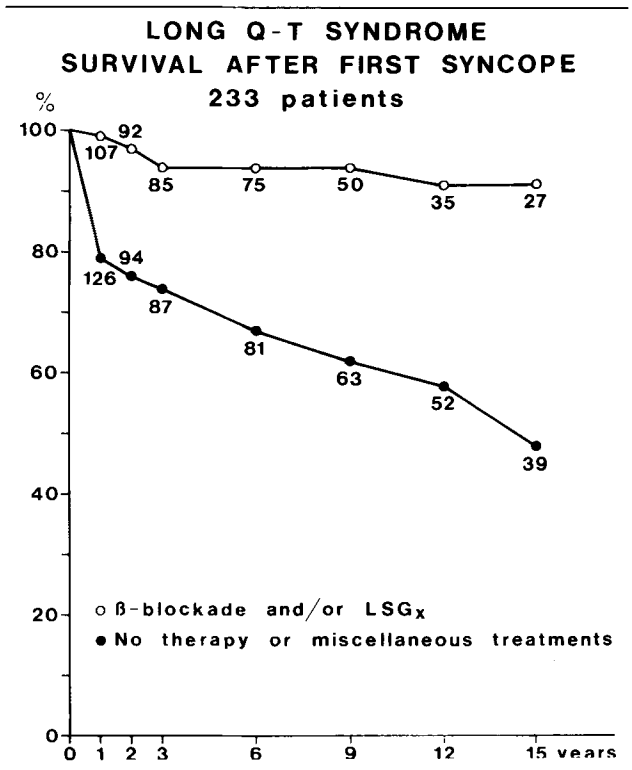

Fig. 6. *Effect of therapy on the survival, after the first syncopal episode, of 233 patients affected by the idiopathic LQTS. The protective effect of beta-adrenergic blockade and of left stellectomy (LSGx) is dramatically evident. For example, the mortality 3 years after the first syncope is 6% in the group treated with antiadrenergic interventions and 26% in the group treated differently or not treated. Fifteen years after the first syncope, the respective mortality is 9% and 53%. Open circle: beta blockade and/or LSGx; filled circle: no therapy or miscellaneous treatments.*

In fact, afterdepolarizations developing from several regions of the heart may result in convergent premature beats resulting in the typical twisting of the QRS.

Torsades de pointes *and afterdepolarizations in the idiopathic LQTS*

Recent experimental evidence has suggested a reappraisal of the issue of which type of afterdepolarizations are more likely to be involved in the genesis of *torsades* in the idiopathic LQTS.

There is a well-established role for the adrenergic nervous system in the genesis of ventricular arrhythmias [30,31]. This clinical form of LQTS is characterized by prolonged QT interval and by syncopal episodes triggered by stressful conditions (physical activity, fear, sudden awakening). The prognosis of untreated symptomatic patients is poor, as the risk for sudden cardiac death approximates 60% within 8–10 years after the first syncope (Figure 6). On the other

hand, the use of antiadrenergic therapy (medical and surgical) has radically modified the prognosis, as the most recent data suggest a 4% mortality over the same time period [32].

As indicated elsewhere [33], it is fair to recall that no placebo-controlled trial is available to support the notion of either pharmacological or surgical antiadrenergic therapy being effective in LQTS and, in all likelihood, it will never be. Indeed, the effect of these interventions in reducing or suppressing syncope/cardiac arrest is so impressive that randomization of these high risk patients to placebo would be unethical and is hardly feasible. The history of medicine abounds with examples of unquestionably effective therapies not tested by a controlled clinical trial, e.g. penicilline and kidney transplant.

In order to define a role for afterdepolarizations in this syndrome, it seems reasonable to analyze the effects of adrenergic activation on the development of afterdepolarizations in the ventricle and in ventricular tissue, and to characterize extensively their behavior. Other experimental models in which afterdepolarizations are induced by a diversity of conditions unlikely to be relevant to LQTS (i.e., Ca^{2+}, digitalis, cesium) are probably not well suited for meaningful extrapolations to this specific clinical condition.

The use of isolated myocytes may have the advantage of limiting the confounding effects of electrotonic propagation in the study of afterdepolarizations; also, the induction of DAD and EAD with catecholamines may mimic the role of sympathetic hyperactivity present in LQTS. Nonetheless, caution is required whenever any experimental model is used to extrapolate data to the clinical setting of LQTS. Indeed, since the pathophysiologic substrate of LQTS is largely unknown, the adequacy of any model in replicating the clinical syndrome cannot be established.

In the preparation of single isolated myocytes [24], administration of isoproterenol evoked afterdepolarizations that, according to their coupling interval, could be classified as both EADs and DADs; however, the two types of afterdepolarizations were not separated on the basis of their frequency-dependency, and they were still simultaneously present at fast (> 180 beats/min) rates (Figure 4). Interestingly, when attempts were made to discriminate EADs and DADs on the basis of their cellular mechanisms, the two types of afterdepolarizations completely overlapped. It has been suggested [34] that EADs are not suppressible by the administration of ryanodine, a blocker of calcium release from the sarcoplasmic reticulum; on the other hand, DADs are promptly inhibited by ryanodine [35]. When, in these isolated myocytes experiments, ryanodine was added in the bath containing isoproterenol, both adrenergically mediated EADs and DADs were simultaneously inhibited; this inhibition was reversible upon washout of ryanodine. The use of low extracellular Na^+, as well as the Na^+/Ca^{2+} exchange blocker, benzamil chloride, also failed to distinguish between these adrenergically induced DADs and EADs. During intense adrenergic activation (10^{-7} M and 10^{-6} M), DADs became multiple and gradually shortened their coupling interval to the preceding beat, to the point that they interrupted the preceding action potential. According to the classic definition of DADs, we could not define these afterdepolarizations occurring during phase 3 of the action potential as DADs, and we elected to call them EAD. However, one is probably still dealing with the same electric event, only with a different name. According to this finding, both types of adrenergically mediated afterdepolarizations would appear to depend on intracellular handling of calcium.

Development of DADs has always been associated with an increase in intracellular Ca^{++} [35]; however, for the less well understood EADs several mechanisms have been advocated.

The classical model used to study EADs involves the use of cesium, a potassium channels blocker that elicits EADs by prolonging repolarization. Since the duration of repolarization depends on the balance between repolarizing and depolarizing currents it is possible that enhancement of Ca^{++} current may lengthen repolarization and favor EADs development. The possibility that also an increased intracellular calcium may be associated with the development of EADs has been proposed by January et al. in a model of EADs induced by the calcium agonist Bay k 8644 [36]. Recent data from our group [19] showed that during reperfusion, a condition associated with increased intracellular Ca^{++}, EADs develop and can be responsible for the development of arrhythmias.

The assessment of a role for afterdepolarizations in the clinical setting is complicated by the need of indirect tools to infer the presence of afterdepolarizations for the electrocardiographic recordings. Preliminary data from our patient population of LQTS suggests that the analysis of Holter recordings can identify T wave alterations which are enhanced by slow heart rate and whose amplitude depends from cicle length in the same way that was demonstrated for EADs [37].

Whether afterdepolarizations actually occur in LQTS patients in response to adrenergic activation has not yet been proven beyond a doubt. On speculative grounds, it can be suggested that they are likely to be mediated by an altered adrenergic innervation of the heart, probably combined with intracardiac ab-

normalities (altered intracellular handling of Ca^{2+}, or altered gating of Ca^{2+} channels, or alterations in K^+ channels). In order to define these cellular abnormalities underlying LQTS beyond speculations, electrophysiologic studies from biopsy specimens from LQTS patients would be required; experimental approaches are at a disadvantage in trying to enlighten the fascinating, and still unknown, intrinsic abnormality of the heart of these patients.

References

1. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. *Arch Mal Coeur* 1966;59:263–272.
2. Brugada P. Torsade de pointes. *PACE* 1988;11:2246–2249.
3. Surawicz B. Electrophysiologic substrate of torsade de pointes: Dispersion of repolarization or early afterdepolarizations? *J Am Coll Cardiol* 1989;14:172–184.
4. Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: A critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* 1988;31: 115–172.
5. Kuo CS, Munakata K, Reddy CP, et al. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983;67:1356–1367.
6. Bonatti V, Rolli A, Botti G. Recording of monophasic action potentials of the right ventricle in long QT syndromes complicated by severe ventricular arrhythmias. *Eur Heart J* 1983;4:168–179.
7. Franz MR, Bargheer K, Rafflenbeul W, et al. Monophasic action potential mapping in human subjects with normal electrocardiograms: Direct evidence of the genesis of the T wave. *Circulation* 1987;75:379–386.
8. Kay GN, Plumb VJ, Arcineigas JG, et al. Torsades de pointes: The long-short initiating sequence and other clinical features: Observations in 32 patients. *J Am Coll Cardiol* 1984;2:806.
9. Bhandari AK, Scheinman M. The long QT syndrome. *Mod Concepts Cardiovasc Dis* 1985;54:45.
10. Nguyen PT, Scheinman M, Seger J. Polymorphous ventricular tachycardia: Clinical characterization, therapy and QT interval. *Circulation* 1986;74:340.
11. Roden DM, Thompson KA, Hoffman BF, et al. Clinical features and basic mechanisms of quinidine-induced arrhythmias. *J Am Coll Cardiol* 1986;8:73A.
12. Cranefield PF. Action potentials, afterpotentials and arrhythmias. *Circ Res* 1977;41:415.
13. Lepeschkin E. Genesis of the U wave. *Circulation* 1957; 15:77–81.
14. Lepeschkin E. Physiologic basis of the U wave. In: Schlant RC, Hurst JW, eds. *Advances in electrocardiography*. New York: Grune & Stratton, 1971:431–437.
15. Hoffman BF, Cranefield PF, Lepeschkin E, et al. Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;196: 1297–1301.
16. Franz MR: Long-term recording of monophasic action potentials from human endocardium. *Am J Cardiol* 1983;51: 1629.
17. Gavrilescu S, Luca C. Right ventricular monophasic action potentials in patients with long QT syndrome. *Br Heart J* 1978;40:1014–1018.
18. Priori SG, Mantica M, Schwartz PJ. Delayed afterdepolarizations elicited in vivo by left stellate ganglion stimulation. *Circulation* 1988;78:178–185.
19. Priori SG, Mantica M, Napolitano C, et al. Early afterdepolarizations induced in vivo by reperfusion of ischemic myocardium. A possible mechanism for reperfusion arrhythmias. *Circulation* 1990;81:1911–1920.
20. Leichter D, Danilo P Jr., Boyden P, et al. A canine model of torsades de pointes. *PACE* 1988;11:2235–2243.
21. Ben-David J, Zipes DP. Differential response to right and left ansae subclaviae stimulation of early afterdepolarizations and ventricular tachycardia induced by cesium in dogs. *Circulation* 1988;78:1241–1250.
22. Damiano BP, Rosen MR. Effects of pacing on triggered activity induced by early afterdepolarizations. *Circulation* 1984;69:1013.
23. Cranefield PF, Aronson RS. Torsade de pointes and other pause-induced ventricular tachycardias: The short-long-short sequence and early afterdepolarizations. *PACE* 1988;11:670.
24. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines in isolated adult ventricular myocytes. *Am J Physiol* 1990;258 (*Heart and Circ Physiol* 27).
25. Priori SG, Yamao KA, Corr PB. Influence of hypoxia on adrenergic modulation of triggered activity in isolated adult canine myocytes. *Circulation*, submitted for publication.
26. Brugada P, Wellens HJJ. Early afterdepolarizations. Role in conduction block, "prolonged depolarization-dependent reexcitation" and arrhythmias in the human heart. *PACE* 1984;8:889–896.
27. Janse MJ, van Capelle FJL, Morsink H, et al. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Evidence for two different arrhythmogenic mechanisms. *Circ Res* 1980;47: 151–165.
28. Schwartz PJ, Malliani A. Electrical alternation of the T wave. Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. *Am Heart J* 1975;89:45–50.
29. Jackman WM, Clark M, Friday KJ, et al. Ventricular tachyarrhythmias in the long QT syndromes. *Med Clin North Am* 1984;68:1079–1109.
30. Schwartz PJ, Priori SG. Adrenergic arrhythmogenesis and the long QT syndrome. In: Vaughan Williams EM, Campbell TJ, eds. *Handbook of experimental pharmacology*. Berlin: Springer Verlag 1989;519–543.
31. Schwartz PJ, Locati E, Priori SG, Zaza A. The long QT syndrome. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology. From cell to bedside*. Philadelphia: WB Saunders, 1990:589–605.
32. Locati E, Schwartz PJ. Prognostic value of QT interval prolongation in post myocardial infarction patients. *Eur Heart J* 1987;8(Suppl. A):121–126.
33. Schwartz PJ, Zaza A, Locati E, Moss AJ. Stress and sudden death; The case of long QT syndrome. *Circulation* Suppl. April 1991 (In press).
34. Marban E, Robinson SW, Wier WG. Mechanisms of ar-

rhythmogenic delayed and early afterdepolarizations in ferret muscle. *J Clin Invest* 1986;78:1185–1192.
35. Wit AL, Rosen MR. Afterdepolarizations and triggered activity. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan E, eds. *The heart and cardiovascular system*. New York: Raven Press, 1986:1449–1490.
36. January CT, Riddle JM, Salata JJ. A model for early afterdepolarizations: induction with the Ca channel agonist Bay K 8644. *Circ Res* 1988;62:563–571.
37. Malfatto G, Rosen MR, Schwartz PJ. Early afterdepolarizations (EAD's) in the idiopathic long QT syndrome. (Submitted for publication).