MINI-SYMPOSIUM:
LONG QT SYNDROME AND TORSADE DE POINTEMES—
IS THE DOCTOR OR THE PATIENT AT FAULT?

Dispersion of Repolarisation and the Autonomic System—Can We Predict Torsade de Pointes?

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Summary. Prediction of the onset of Torsade de Pointes (TdP) is a challenge for clinicians, because the list of drugs affecting myocardial repolarisation is continuously increasing. Alterations in the activity of autonomic nervous system and abnormalities in ventricular repolarisation are key features both as triggers and as markers for vulnerability to TdP. Recent molecular genetic studies have shown that autonomic nervous system has channel and gene specific influences on vulnerability to TdP. New analysis techniques in quantifying the dispersion of repolarisation have also been developed. QT interval dispersion, defined as a difference between the maximum and minimum QT interval measured from the standard 12-lead electrocardiogram (ECG), is one such method. In preliminary studies, QT dispersion has provided more accurate information on the risk for TdP than the measurement of the length of QT interval from a single ECG lead. Unfortunately, QT dispersion is entailed with some conceptual and methodological problems, which impairs its widespread clinical utility in risk stratification. Despite advances in the understanding of the role of autonomic nervous system as a trigger of TdP in specific gene mutations and improved clinical methods in detecting repolarisation abnormalities, accurate and reliable prediction of the onset of TdP still remains an unresolved clinical problem in individual cases.

Key Words. autonomic tone, QT interval

Introduction

Torsade de Pointes (TdP) is a rapid polymorphic ventricular tachycardia with a distinctive, twisting configuration, typically associated with long QT syndrome (LQTS), either congenital or acquired. In LQTS, abnormal or altered function of ion channels at the myocardial cell membrane causes prolongation of the myocardial repolarisation. This malfunction may be caused by mutations in the genes encoding specific ion channels, by drugs or by metabolic abnormalities. To date, six genotypes (LQT1 to LQT6) have been identified in the congenital LQTS [1]. In acquired LQTS, drugs most commonly cause abnormality in the ion channel function, and the list of drugs that may impair the channel function is continuously increasing [2]. Therefore, identification of the drugs that may produce LQTS and of individuals who might develop TdP is an important challenge for clinicians.

Symptoms caused by TdP vary from palpitation or syncope to cardiac arrest. Symptoms are generally related to the duration of TdP. Most often TdP stops spontaneously, but in some cases longer runs may degenerate into ventricular fibrillation. Because of a potential for sudden cardiac death, scientists and clinicians have attempted to find methods for prediction of the onset of TdP far in advance before its onset. The transient nature of the condition and the unpredictability of the occurrence of TdP have confounded these attempts. This arrhythmia cannot be induced e.g. by programmed electrical stimulation or by any other clinically useful intervention.

Some information has been obtained on the role of autonomic nervous system as a trigger of TdP in various forms of LQTS. Heterogeneity in the ventricular repolarisation has long been recognised to increase the vulnerability for TdP. Therefore, new methods have been introduced for identifying the dispersion of repolarisation. The role of both autonomic nervous system and measurement of dispersion of repolarisation have gained increasing attention in the genesis of TdP and also in prediction of this arrhythmia.

Electrophysiological Mechanisms of TdP

In spite of extensive work of many electrophysiological research groups, there is no universally accepted mechanism that could account for all various forms of TdP. The potential mechanisms have been extensively
reviewed in the recent literature [3–7]. Majority of experimental and clinical studies has implicated that early afterdepolarisations (EADs) contribute to the onset of TdP [8,9]. EADs are oscillations of the transmembrane potentials during the myocardial repolarisation phase, and can give rise to new action potentials when they reach a critical threshold for activation of a depolarising current. EADs can be seen as prolonged QT intervals, bizarre T waves or U waves on a standard 12-lead electrocardiogram (ECG) [8,9]. After reaching the critical threshold creating new action potentials, the EADs may appear as ectopic beats on the ECG. When repetitive firing occurs due to EADs, the tachyarrhythmia is defined to develop as a triggered activity mechanism. EADs can also augment heterogeneity in repolarisation between neighbouring myocardiurn, which can lead to the formation of new action potentials via electronic interaction between areas that are still inexcitable and those that have recovered from refractoriness [10]. The latter mechanism is re-entrant rather than triggered activity. Thus, EADs have been considered to have importance in the genesis of TdP, either via triggered activity or re-entry, or combination of these two [11]. The widely accepted theory is that EADs causing triggered activity may initiate TdP and re-entrant mechanisms may be responsible for its perpetuation.

The background for LQTS and development of EADs is a reduction in net outward ionic current and/or an increase in inward ionic current at the cellular level during repolarisation phase [12]. Intrinsic transmural heterogeneity in the density of the various ion channels has also been observed [4]. Block or activation of these channels has different effects on the action potential duration of four different cell types: Purkinje cells, subendocardial myocytes, midmyocardial M cells, and subepicardial cells. EADs have been shown to occur preferentially in M cells and/or Purkinje cells.

**Triggers of Torsade de Pointes**

Onset of TdP in congenital LQTS has been traditionally related to enhanced adrenergic or stressful states, whereas the onset of TdP in acquired LQTS is usually related to pauses in cardiac interbeat intervals. Categorising of congenital LQTS as purely “adrenergic” and acquired LQTS as purely “pause dependent” is arbitrary, however, because TdP is often preceded by a pause in congenital LQTS and adrenergic stimulation may also facilitate drug induced TdP [13–15]. Ambulatory ECG recordings at the time of onset of TdP have shown that an increase of average heart rate usually precedes the onset of TdP [13]. In the majority of cases a short-long-short sequence of cardiac interbeat intervals triggers the TdP both in acquired and congenital LQTS [13–15]. A combination of increased heart rate, probably caused by enhanced adrenergic drive, and short-long-short sequences, usually caused by ectopic beats followed by a compensatory pause, is a typical finding preceding the onset of TdP.

In some cases of TdP, bradycardia precedes the onset of TdP. In these cases, prolongation of QT interval, occurrence of bizarre T-waves or prominent T-waves is often observed before the arrhythmia onset. Vulnerability to TdP in acquired LQTS is also related to other factors, such as female gender, irregular rhythm, and hypopotassemia and/or hypomagnesemia, cardiac hypertrophy and dysfunction [1–5,16]. Despite the typical ECG characteristics and clinical features related to TdP both in congenital and acquired TdP, these factors do not offer very much for prediction of the onset of TdP in individual subjects, because dynamic changes in HR and QT behaviour, or electrolytes are usually not continuously monitored in clinical practice. Therefore, attempts to find particular features that predispose to the onset of TdP in individual subjects are of major importance. Some new information on the triggers and predictors of TdP has been obtained from molecular genetic studies in congenital LQTS and from various analysis techniques of ventricular repolarisation.

**Autonomic Nervous System and Onset of Torsade de Pointes**

Autonomic nervous system is considered to be an important factor as a trigger of TdP both in congenital and acquired LQTS. Therapeutic benefit of beta-blockers or left cardiac sympathectomy is evident in congenital LQTS [17–19]. Recent molecular genetic studies have now provided some new information on the genotype-phenotype interactions in the congenital LQTS and on the effects of adrenergic modulation on the function of specific ion channels [20,21]. Table 1 summarises the current knowledge of the role of autonomic nervous system as a trigger of TdP in various conditions.

**Clinical findings on the role of autonomic nervous system**

A large analysis of genotyped symptomatic LQTS patients showed that life-threatening arrhythmias tend to occur in a gene-specific manner in the patients with congenital LQTS [22]. Sympathetic activation caused by physical or emotional stress was the trigger for 87% of lethal cardiac events in LQT1. In contrast, sympathetic activation was observed in 56% of LQT2 patients and in only 32% of LQT3 patients. In LQT3, a larger proportion (39%) of arrhythmia events occurred at sleep/rest. Auditory stimuli were relatively common triggers in LQT2 patients, and swimming was particularly frequent among LQT1 patients. All these various stimuli may cause specific autonomic responses, which can then trigger TdP only in individuals with specific mutations of the ion channels. For example, diving and swimming (face immersion) may cause a concomitant vagal and sympathetich activation, which seems to be particularly hazardous for LQT1 patients [22,23]. Auditory stimuli may in turn result in an abrupt change in