Acquired Long QT Syndrome

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When he first described torsades de pointes Dessertenne did not know that there are many causes of this arrhythmia. Whilst torsades de pointes can be part of both congenital and acquired long QT syndromes, acquired long QT syndrome from pharmacological drugs is by far the most common cause of this arrhythmia. The cloning of cardiac ion channels has improved our understanding of the role of ion channels in mediating cardiac repolarization and in the pathomechanism of drug-induced long QT syndrome and TdP. As a result, increasingly more drugs have been discovered to be proarrhythmic and potentially cause sudden cardiac death. However, clinical assessment of such proarrhythmic risk is hard, if not impossible, to undertake. At times, the potential risk of proarrhythmia is often not detected during development of the compound. Frequently, the medical profession may need to rely on post-marketing surveillance and anecdotal case reports to assess the proarrhythmic risk of a new pharmacological compound, especially of a nonantiarrhythmic drug. A comprehensive literature on acquired long QT syndrome, from basic science to clinical cardiology is lacking.

This book is written with the intention of providing a detailed review on acquired long QT syndrome, from drug-induced QT prolongation to cardiac causes and noncardiac causes of QT prolongation. Detailed attention is paid to the mechanism of drug-induced QT prolongation and the clinical methodology of measuring myocardial repolarization which is crucial in the assessment of the proarrhythmic risk of a particular drug. We attempted to provide a thorough review on most of the drugs that have been reported to cause QT prolongation and/or torsades de pointes and provided our perspective towards drug-induced proarrhythmia.

The field of long QT syndrome, both congenital and acquired, is clearly advancing rapidly and they are not mutually exclusive. Indeed, whilst congenital long QT syndrome has been used as a model for explaining the proarrhythmic effects of many drugs, some patients who are carriers of the genetic mutations for congenital long QT syndrome (form-fruste of long QT syndrome) have their conditions unmasked by proarrhythmic drugs. Further insight will soon be available on the understanding of particular susceptibility to drug-induced QT prolongation and/or torsades de pointes. We hope that this book will be particularly useful for the cardiologist, electrophysiologist, pharmacologist, physician and pharmaceutical industry scientist.
CHAPTER 1

Introduction

Torsades de pointes

In 1966, Francois Dessertenne described the electrocardiographic form of polymorphic ventricular tachycardia, which he termed “torsades de pointes” (TdP) [1,2]. The word “torsades” refers to an ornamental motive imitating twisted hairs or threads as seen on classical architectural columns, and “pointes” referred to points or peaks. To further demonstrate his description, he rotated a comb along its long axis (Fig. 1.1) to show how the points of the teeth and the intermediary gap simulated the asymmetrical electrocardiographic waves of this type of tachycardia. In French, TdP means “twisting of points”, and this refers to the continuously changing polarity and amplitude of the tachycardia QRS complexes. In the seminal article, Dessertenne made no attempt to suggest the mechanism of TdP and, until recently, there has been considerable conjecture as to the pathophysiology of this arrhythmia.

Since the original work by Dessertenne, it has been well recognized that many conditions may cause prolonged or abnormal repolarization (i.e., QT interval prolongation and/or abnormal T or T/U wave morphology), which is associated with TdP. Essentially, TdP may be part of either congenital or acquired long QT syndromes (LQTS). In the recent years, there is considerable renewed interest in the assessment and understanding of ventricular repolarization and TdP. There are several reasons for this. Firstly, the cloning of cardiac ion channels has improved the understanding of the role of ion channels in mediating cardiac repolarization, the pathophysiological mechanism of LQTS (congenital and acquired forms), and the pathogenesis of TdP. Secondly, there has been considerable enthusiasm for the development and use of class III antiarrhythmic drugs, which prolong repolarization and cardiac refractoriness. Unfortunately, many drugs that alter repolarization have now been recognized to increase the propensity to TdP, which is associated with syncope and can lead to ventricular fibrillation and sudden death. Finally, an increasing number of drugs, especially noncardiac drugs, have been recognized to delay cardiac repolarization and to share the ability with class III antiarrhythmics to occasionally cause TdP.

Is TdP an arrhythmia or syndrome?

Since the time of its original description, the precise definition of “torsades de pointes” has been controversial. For Dessertenne, etiological factors were not
an obligatory part of the definition, but rather an aid to the diagnosis. To some cardiologists, TdP is merely as an arrhythmia electrocardiographically similar to that of polymorphic ventricular tachycardia, with a set of recognized causes (congenital QT prolongation, drugs, hypokalaemia, heart block, etc.) [3]. Others described TdP as a syndrome, comprising the arrhythmia, prolonged QT interval during sinus rhythm, and a specific set of antecedent etiologies, which are included within the definition [4]. Brugada proposed that the diagnosis of TdP should require the initiation of the tachycardia by a late extrasystole [5]. Surawicz suggested that TdP is a polymorphic ventricular tachycardia associated with a prolonged QT interval or increased U wave amplitude which is amenable to suppression by an increase in heart rate [6]. El-Sherif and Turito agreed that TdP should be reserved for use in polymorphic ventricular tachycardia associated with long QT syndrome [7]. On the other hand, Coumel et al. mentioned that not all long QT syndrome patients with polymorphic ventricular tachycardia have a characteristic TdP configuration, and that the classic configuration of TdP can be seen without a prolonged QT interval [8]. At the end of the spectrum of views, Curtis proposed that the term TdP should be abandoned because of its confusion as to whether it represents a unique arrhythmia or clinical syndrome [9].

In practice, TdP is described as a unique form of polymorphic ventricular tachycardia that is part of a syndrome associated with QT prolongation, and usually with one or more well recognized etiological factors. In other words, it is a “chimera”—part arrhythmia and part syndrome [10]. Thus, the characteristic pattern of TdP with rapid bursts of ventricular complexes, appearing to twist around the isolectric axis should immediately alert the clinician to the high probability of an underlying cause that should be removed or corrected, especially if it is associated with other features including QT prolongation, T wave alternans, and/or short-long-short ventricular sequence of initiation. While TdP is usually self-limiting, it may degenerate into or provoke ventricular fibrillation and sudden death (Fig. 1.2).
Acquired QT prolongation and TdP

The congenital long QT syndromes (Fig. 1.3), which include the Jervell–Lange–Nielson syndrome (with deafness) and the Romano–Ward syndrome (without deafness), are associated with TdP and/or sudden death. The Jervell–Lange–Nielson syndrome is a recessively inherited condition whereas the Romano–Ward syndrome is an autosomal dominant condition, although there is now evidence that the inherited traits of both syndromes are not mutually exclusive. Modern molecular techniques have identified the mutations in genes encoding cardiac ion channels that cause long QT syndrome (Table 1.1), although the
Table 1.1 Genetic mutations and clinical presentations of congenital long QT syndrome.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Chromosome locus</th>
<th>Gene affected</th>
<th>Ion channel affected</th>
<th>T wave</th>
<th>Typical clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal dominant (Romano–Ward)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KVLQT1 (KCNQ1)</td>
<td>$I_{\text{Ks}}$ $\alpha$ subunit</td>
<td>Broad</td>
<td>No QT change with exercise, syncope during physical or emotional stress</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35–36</td>
<td>HERG</td>
<td>$I_{\text{Kr}}$ $\alpha$ subunit</td>
<td>Notched</td>
<td>Normal QT shortening with exercise, syncope during stress, rest or auditory stimuli</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21–24</td>
<td>SCN5A</td>
<td>$I_{\text{Na}}$</td>
<td>Peaked and delayed onset</td>
<td>Supra-normal QT shortening with exercise, syncope during sleep or rest</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25–27</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Bizzare T wave</td>
<td>Severe bradycardia and atrial fibrillation</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1–22.2</td>
<td>MinK (KCNE1)</td>
<td>$I_{\text{Kr}}$ $\beta$ subunit</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22.1–22.1</td>
<td>MiRP1 (KCNE2)</td>
<td>$I_{\text{Kr}}$ $\beta$ subunit</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LQT7</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Autosomal recessive (Jervell–Lange–Nielsen)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JLN1</td>
<td>11p15.5</td>
<td>KVLQT1 (KCNQ1)</td>
<td>$I_{\text{Ks}}$ $\alpha$ subunit</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>JLN2</td>
<td>21q22.1–22.2</td>
<td>MinK (KCNE1)</td>
<td>$I_{\text{Kr}}$ $\beta$ subunit</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>JLN3</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>JLN4</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
genetic defects in about 20% of patients are still unknown. The clinically manifested condition of congenital LQTS is rare.

The acquired form of LQTS is more common. It has many causes (Table 1.2) of which the most likely is medication. A steadily increasing number of drugs (cardiac and noncardiac) have been reported to cause QT prolongation (Fig. 1.4), TdP, ventricular arrhythmias and sudden death. Naturally, this has troubled both the drug regulatory authorities and medical communities, especially since many of these drugs do not have cardiac indications but instead are widely prescribed for self-limiting, non life-threatening disease. The risk of fatal ventricular arrhythmia is potentially large and the pro-arrhythmic risks of many of these drugs were not recognized until many years after they were marketed.

It is still open to speculation whether TdPs occurring due to congenital and acquired LQTS are completely separate entities. Patients with subclinical

<table>
<thead>
<tr>
<th>Table 1.2 Selected (nondrug-related) causes of acquired long QT syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart disease</strong></td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmias</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Bradycardia (SA nodal dysfunction, AV block)</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td><strong>Metabolic abnormalities</strong></td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
</tr>
<tr>
<td><strong>Endocrine disorder</strong></td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
</tr>
<tr>
<td><strong>Intracranial pathology</strong></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>Head injury</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Anorexia nervosa/starvation</td>
</tr>
<tr>
<td>Bulemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td><strong>Liquid protein diet</strong></td>
</tr>
<tr>
<td><strong>Human immunodeficiency virus (HIV) infection</strong></td>
</tr>
</tbody>
</table>

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congenital LQTS as well as patients with non drug-related acquired LQTS are more susceptible to the development of drug-related TdP. A different degree of propensity to the initiation of TdP likely also exists between different drugs. While some drugs are likely to cause TdP in patients with relatively undisturbed repolarization, other drugs are probably capable of triggering TdP only in subjects with an underlying abnormality, e.g., subclinical congenital defect of repolarization channels.

Hence, although there are some, presumably mainly autonomic mechanisms that lead to QT interval prolongation in practically every subject (e.g., the QT interval prolongation during sleep), the pathological mechanisms and/or drugs with repolarization involvement that lead to acquired LQTS may only manifest in subjects who already have some congenital (possibly sub-clinical) abnormality of cardiac repolarization. In this sense, there is a

Fig. 1.4 ECGs of a 63-year-old-female patient with thioridazine-induced ventricular fibrillation cardiac arrest while in hospital. She was successfully resuscitated and this is the ECG performed immediately after the cardiac arrest (top). Note the QTc interval was 619 ms and her serum potassium level at this time was 3.3 mmol/L. The QTc interval returned to normal (399 ms) after the withdrawal of thioridazine and correction of her serum potassium level to 4.4 mmol/L (bottom). Her subsequent coronary angiogram was normal.
whole spectrum of drugs and pathological stimuli differing in their propensity to cause acquired LQTS. In the drug-induced LQTS, some compounds caused TdP in an appreciable number of subjects (e.g., the TdP incidence on quinidine has been reported between 2.0% and 8.8% [11–14]) while other compounds cause TdP extremely rarely, only in specific subjects in whom the drug effect is combined with a highly individual repolarization abnormality (e.g., while fexofenadine is a very safe drug, it caused TdP reproducibly in a particular subject who presumably had an underlying abnormality making him particularly susceptible for such a highly unusual reaction [15]). Therefore, it is not very reasonable to classify drugs into those which do and those which do not cause TdP. Rather, different drugs should be characterized by their propensity to cause the arrhythmia, ranging near zero for the very safe drugs to the induction in up to approximately 10% patients for the most repolarization active antiarrhythmic drugs.

References
CHAPTER 2

Mechanisms of acquired QT prolongation and torsades de pointes

Normal ionic and molecular basis of the cardiac action potential

The cardiac action potential is generated by the changing transmembrane permeability to ion currents such as Na\(^+\), Ca\(^{2+}\) and K\(^+\). Like all living cells, the potential inside a myocyte cell is negative compared to the outside (resting transmembrane potential of \(-80\) to \(-90\) mV). However, cardiac cells are excitable and when appropriately stimulated, the ion channels within the cell membrane open and close sequentially. This changes the transmembrane ion permeability and leads to the sequential development of the transmembrane potential that is called the action potential (Fig. 2.1).

The initial depolarization (phase 0) is triggered by the rapid inward sodium (\(I_{Na}\)) and the L- and T-type calcium currents (\(I_{Ca-L}\) and \(I_{Ca-T}\)), which change the cell potential from \(-90\) mV to \(+30\) mV [1]. The transient outward \(I_{to}\) potassium current

![Fig. 2.1 Cardiac ionic currents and their relationship with action potential (modified from [2]).](image)

\[ \text{Na}^+ \text{ Current } \]
\[ \text{L-type Ca}^{2+} \text{ Current } \]
\[ \text{T-type Ca}^{2+} \text{ Current } \]
\[ \text{Na}^+\text{-Ca}^{2+} \text{ exchange } \]
\[ I_{T01} (4-\text{AP-sensitive}) \]
\[ I_{T02}(\text{Ca}^{2+}\text{-activated}) \]
\[ I_{ks} \]
\[ I_{kr} \]
\[ I_{Kur} \]
\[ I_{Cl} \text{ or } I_{kp} \]
\[ \text{Inward rectifier, } I_{k1} \]
\[ \text{Pacemaker current, } I_{f} \]
current is responsible for the slight repolarization immediately after the overshoot (phase 1). During the following plateau phase (phase 2), the cell potential is maintained by a balance between the inward L-type calcium current ($I_{\text{Ca-L}}$) and the electrogenic sodium–calcium exchange current ($I_{\text{NaCa}}$), and the outward $I_{\text{to}}$ current. The repolarization phase (phase 3) of the myocyte is driven predominantly by outward movement of potassium ions, carried as the rapid ($I_{\text{Kr}}$) and slow ($I_{\text{Ks}}$) components of the delayed rectifier potassium current. The diastolic depolarization (phase 4) results from a combination of the decay of the outward delayed rectifier $I_{\text{Kr}}$ and $I_{\text{Ks}}$ currents, which maintains the resting potential at approximately $-90 \text{ mV}$, and the activation of the inward pacemaker current ($I_{\text{f}}$) and the inward sodium background leak current ($I_{\text{Na-B}}$). A variety of other different potassium channel subtypes are also present in the heart [2]. Pharmacological blocking and opening of each of these channels has a different effect on the action potential (Fig. 2.2).

**Mechanism of acquired QT prolongation and TdP**

**Early after-depolarization and dispersion of ventricular repolarization**

Prolongation of the action potential can be achieved by a reduction of the outward currents, particularly the outward delayed rectifier, $I_{\text{Kr}}$ or $I_{\text{Ks}}$ potassium currents and/or enhancement of the inward currents during phase 2 and 3 of the action potential. Among the potassium currents, $I_{\text{Kr}}$ is most susceptible to pharmacological influence. In all presently known drug-induced acquired long QT syndrome (LQTS), the blockade of the $I_{\text{Kr}}$ current is at least in part responsible for action potential prolongation and proarrhythmia. Blockade of $I_{\text{Kr}}$ current results in the reduction in net outward current, a slowing of repolarization, prolongation of the action potential and clinically, QT interval prolongation and development of T- or U-wave abnormalities on the surface ECG (Fig. 2.3). The prolongation of repolarization...
may result in subsequent activation of an inward depolarization current (ICa,L and INa), which generates early after-depolarizations, which in turn promote triggered activity at the end of repolarization. This occurs preferentially in the Purkinje fibers and the mid-myocardial M cell population (compared to epicardial and endo-cardial cells) [3]. When accompanied by the presence of a markedly increased dispersion of repolarization, this may induce re-entry and provoke TdP, which is then sustained by further re-entry or spiral wave activity (Fig. 2.4). Thus, the presence of early after-depolarizations and dispersion of repolarization are prerequisites for the initiation and maintenance of TdP.

One reason why such activity is more readily induced in the Purkinje fibers and M cells may be related to the fact that the resting membrane potential in Purkinje fibers is more positive than that in the ventricles and the blockade of IKr channel is voltage dependent, with more block in depolarized tissue [4,5]. This may lead to dispersion of refractoriness between the two tissue types which is potentially arrhythmogenic. Similarly, compared to subendocardial or subepicardial cells, M cells show more pronounced action potential prolongation in response to IKr blockade [6]. This property results in a marked dispersion of repolarization (i.e., heterogeneous recovery of excitability), creating a zone of functional refractoriness in the midmyocardial layer, which may be the basis of the re-entry that sustains TdP.

**Myocardial M cell**

The term “M cell” refers to a recently described subpopulation of mid-myocardial cells with electrophysiological properties resembling those of Purkinje fibers rather than those of other myocardial cells. Differential sensitivity of M cells relative to epicardial and endo-cardial cells to interventions (e.g., slowing of heart rate) or drug exposure may increase heterogeneity of repo-
larization across the ventricular wall (i.e., transmural dispersion of action potentials), and provide an anatomic and physiologic substrate for TdP, via transmural re-entry [3,7]. M cells have a weaker $I_{Ks}$ potassium current and an increased late $I_{Na}$ sodium current, both of which are believed to contribute to 

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**Fig. 2.4** Arrhythmogenesis of torsades de pointes.

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Non-sustained Syncope

Torsades de Pointes

Sustained Degenerates into VF & cardiac arrest

---

Blockade of $I_{Kr}$ Channels

↑Intracellular K current & ↓ net repolarizing current

↑action potential duration in Purkinje fibers and M cells relative to epi- and endocardial cells

↑Heterogeneity (dispersion) of intracardiac repolarization

Unidirectional block & intramural reentry circuit

Early after-depolarization

Triggered activity

Mechanisms of acquired QT prolongation and TdP
the long action potential duration (compared with that of epi- and endocardial cells) and sensitivity of the M cell to QT prolonging drugs and development of early after-depolarizations [8].

Experimental studies have shown that M cells are directly implicated in the genesis of QT prolongation and related T/U wave abnormalities, and initiation of TdP acquired long QT syndrome. Shimizu and Antzelevitch examined the transmembrane action potential from epicardial, midmyocardial and endocardial sites simultaneously with a local transmural ECG using an arterially perfused canine left ventricular wedge preparation [9]. They have shown that the midmyocardial region is the last to repolarize and marks the end of the T wave both in normal conditions and under experimental QT prolongation (Fig. 2.5). Furthermore, induction of beat-to-beat changes in T wave amplitude and/or morphology (T wave alternans) under long QT conditions in the perfused wedge showed that this phenomenon was caused by a parallel beat-to-beat alternation of the action potential duration (repolarization) in the midmyocardial region, leading to an exaggeration of transmural dispersion of repolarization during alternate beats which will favor the

**Fig. 2.5** The midmyocardial region is the last to repolarize and marks the end of the T wave both in normal conditions and under experimental QT prolongation. ATX-11, sea anemone toxin which augment the late sodium current (ina) and produce long QT conditions similar to those caused by the defect in SCN5A, which is responsible for the congenital LQT3 syndrome (adapted from [9]).
development of TdP (Fig. 2.6) [9]. It has thus been suggested that TdP is initiated by early after-depolarization-induced triggered activity in the M cells and is maintained by a re-entrant mechanism, created by an increase in the spatial dispersion of repolarization in the abnormal midmyocardium [10].

**Short-long-short ventricular cycle**

Kay *et al.* first described a characteristic short-long-short ventricular initiating sequence prior to the onset of TdP, particularly in acquired long QT syndrome (Fig. 2.7) [11]. However, the development of a postpause T- or U-wave abnormality is also seen when the arrhythmia is initiated [12]. The first ventricular complex of the sequence is generally a ventricular ectopic beat or the last beat of a salvo of ventricular premature beats. This is followed by a postectopic pause and a subsequent sinus beat. The sinus beat frequently has an exaggerated U wave. A premature ventricular beat arises from this exaggerated U wave and precipitates the onset of TdP. (Some actually speculate that this unusually large U wave is not a true U wave but a bizarre depolarization pattern due to an after-depolarization that captures a large myocardial region.) This stereotypical short-long-short cycle length changes and the presence of a postpause U wave constitute the typical pattern of initiation of TdP. This observation was subsequently confirmed by Roden *et al.* who summarized the pattern as “short cycle–long cycle–long QT–late premature ventricular complex” [13,14].

Both the abnormal T and U waves and a single ectopic impulse that follow a postectopic pause may be regarded as a warning sign of an impending TdP.