Acquired QT prolongation and Torsades de Pointes: a review and case report

Alastair Gray, Conor McQuillan

Royal Victoria Hospital Belfast

Introduction

As early as the 1920's it was noted that several drugs including quinidine were associated with syncope and sudden cardiac death however the mechanism of this adverse effect initially remained elusive. Further work in this field in the 1950's identified several families with prolongation of the QT interval and an increased incidence of sudden death. By 1964 Seltzer and Wray identified that quinidine induced syncope was due to polymorphic ventricular tachycardia and in 1966 Dessertenne reported a case of bradycardia dependent ventricular tachycardia.(1) He described characteristic ventricular complexes with beat by beat axis variation and termed this Torsades de Pointes (TDP). It is now recognised that TDP represents a specific form of potentially life threatening ventricular arrhythmia occurring in the setting of QT interval prolongation. Whilst normally short lived and self-terminating, quick and successive runs of TDP can degenerate into ventricular fibrillation and cardiac arrest.

TDP is characterised by ventricular complexes of varying amplitude and contour (polymorphic) that rotate around the isoelectric line in the setting of QT interval prolongation. There are now several recognised inherited genetic disorders that either predispose to or prolong the QT interval and increase the risk of arrhythmia and sudden cardiac death, the so called Long QT syndromes (LQTS). Separate to this group of genetic conditions are the acquired disorders which may arise due to precipitating conditions such as electrolyte imbalance or from administered medications. TDP in the setting of acquired LQTS shall form the focus of this report

QT Interval

Before considering the mechanism of TDP it is essential to accurately define the QT interval and its measurement. The QT interval reflects the action potential duration and is the time from the beginning of ventricular depolarisation to the end of repolarisation. This is calculated from the surface electrocardiogram by measuring from the beginning of the QRS complex to the end of the T wave, defined as the intercept between the isoelectric line and a tangent line drawn to the steepest part of the T wave. (2,3) As the QT interval is affected by heart rate several formula have been defined to enable correction for rate (QTc). The two most commonly used formulae being Fredericia's cube root formula and Bazett's square root formula. The R-R interval of the preceding QT interval is measured to enable rate correction with these methods.

Bazzet's square root formulae

$$QTc = QT/\sqrt{RR}$$

Fredericia's cube root formula

$$QTc = QT/\sqrt[3]{RR}$$

From these equations it is evident that as the ventricular rate slows the QT interval prolongs. Whilst Bazzett's formula is the most commonly used it is recognised that in patients with tachycardia this equation may over estimate the degree of QT prolongation whilst in those with bradycardia it may result in apparent QTc shortening.(4) Fredericia's formula is less prone to this degree of correction variation but both methods still rely heavily on accurate RR and QT interval measurement. Whilst conceptually simple these measurements can be difficult. For example, from a single 12 lead ECG, measurement of the same QRS complex in different leads may yield a variation of up to 50ms in the QTc. This dispersion of repolarization is thought to represent differences in regional action potential duration.

In addition the presence of U waves may further complicate the measurement of QTc. In general it is accepted that if the U wave is small (<25 -50% of the preceding T-wave) it should not be included in the measurement.(1)

Despite these difficulties in measurement normalised values for QTc have been defined based on age and sex. For adult males the QTc is considered prolonged when it measures greater than 440ms and in females greater than 460ms. A recent American Heart Association scientific statement has however suggested that the 99th centile may represent a more appropriate upper limit of normal with 470ms for males and 480ms for females.(5)

Whilst the QTc is dependent on heart rate it is also recognised that significant diurnal variation of up to 100ms may occur. Additionally the QT interval may be affected by, sympathetic activity, drugs, electrolyte imbalances, metabolic disturbances and alterations in cardiac loading.

Other Risk Factors

In addition to QT prolonging medications, there are also a number of risk factors which predispose to TDP and it is often the combination of these that leads to the development of this arrhythmia. (1,2,4,7)

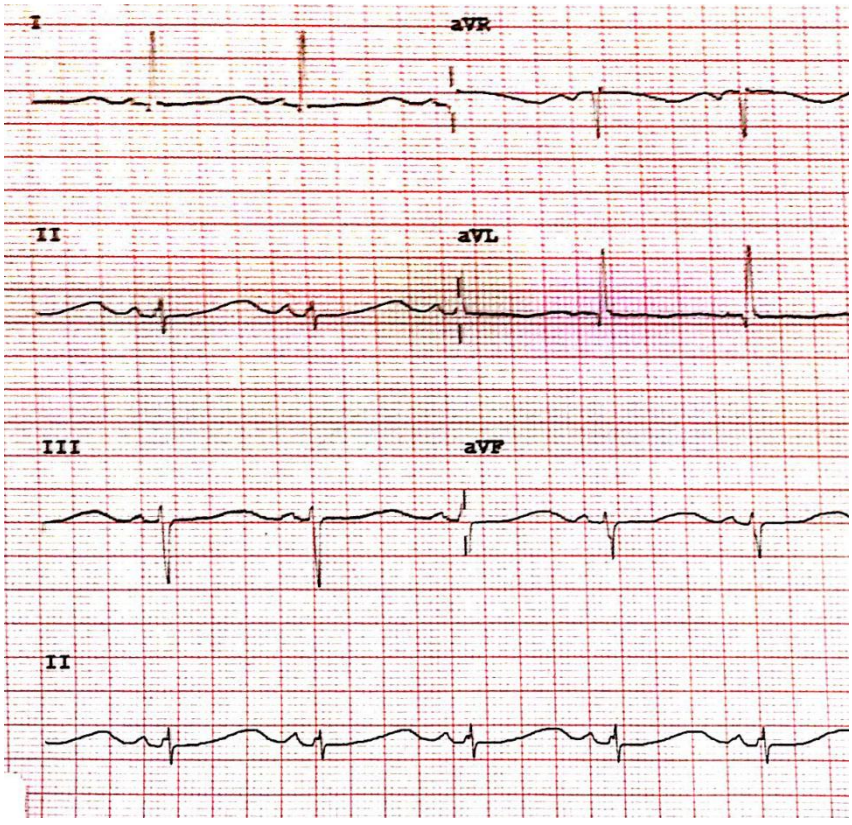
- Age >65 years
- Electrolyte imbalance
    - hypokalaemia, hypomagnesaemia
- Congenital long QT
- Bradycardia
- Cardioversion
- Cardiac disease
- Female gender
- Infection

Case Report

With an underlying diagnosis of acute myeloid leukaemia our elderly female patient was admitted under the haematology team with her sixth episode of neutropenic sepsis, on this occasion secondary to conjunctivitis and subsequent orbital cellulitis. Her admission potassium was noted to be 2.8mmol/ml and was attributed to a recent gastroenteritis. She was commenced on Tazocin and due to the suspicion of a superimposed lower respiratory tract infection had clarithromycin added to her regimen.

Due to significant nausea she was commenced on 8mg TDS of ondansetron. Her pre-admission medication included escitalopram and haloperidol. She had an un-witnessed syncopal episode on the haematology ward and the reviewing house officer became concerned due to a further fall in potassium 2.6mmol/mL, low magnesium (0.46mmol/mL) and visible prolongation of her QT interval on her surface electrocardiogram. (Figure 1)

Figure 1: QTc = 586ms



Whilst arranging transfer to the cardiology ward she developed further pre-syncopal symptoms which preceded a cardiac arrest with loss of output. Runs of non-sustained ventricular arrhythmia (Figure 2) and TDP (Figure 3) were identified. Fortunately she was successfully resuicitated.

Figure 2: NSVT

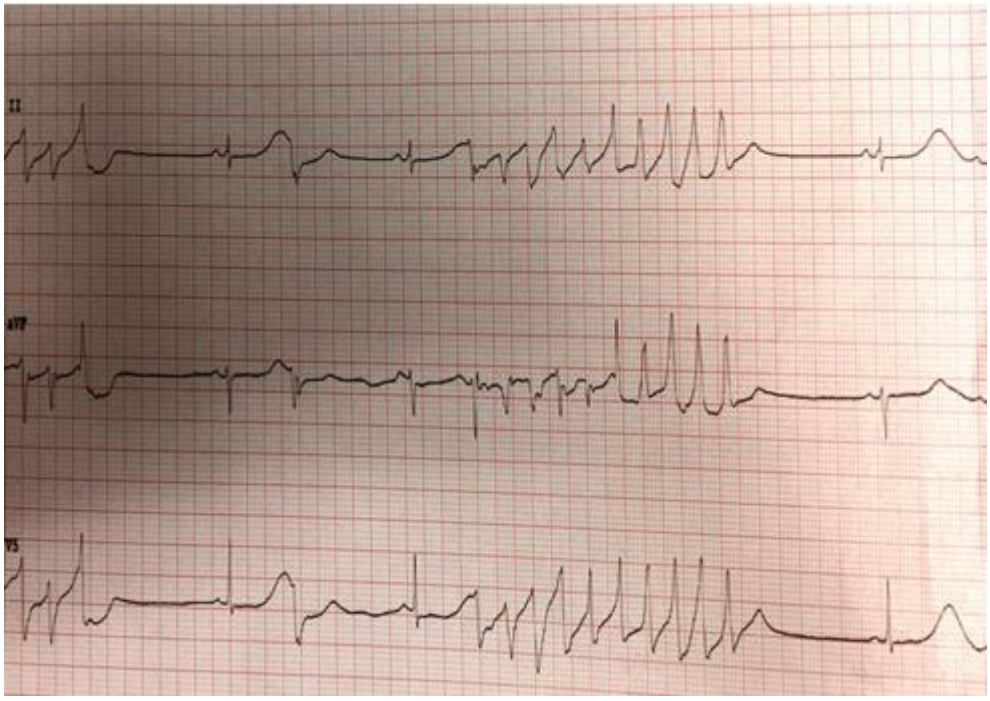
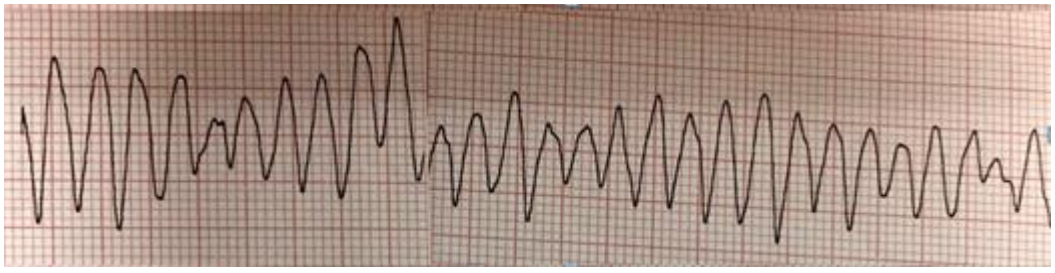


Fig 3: TDP

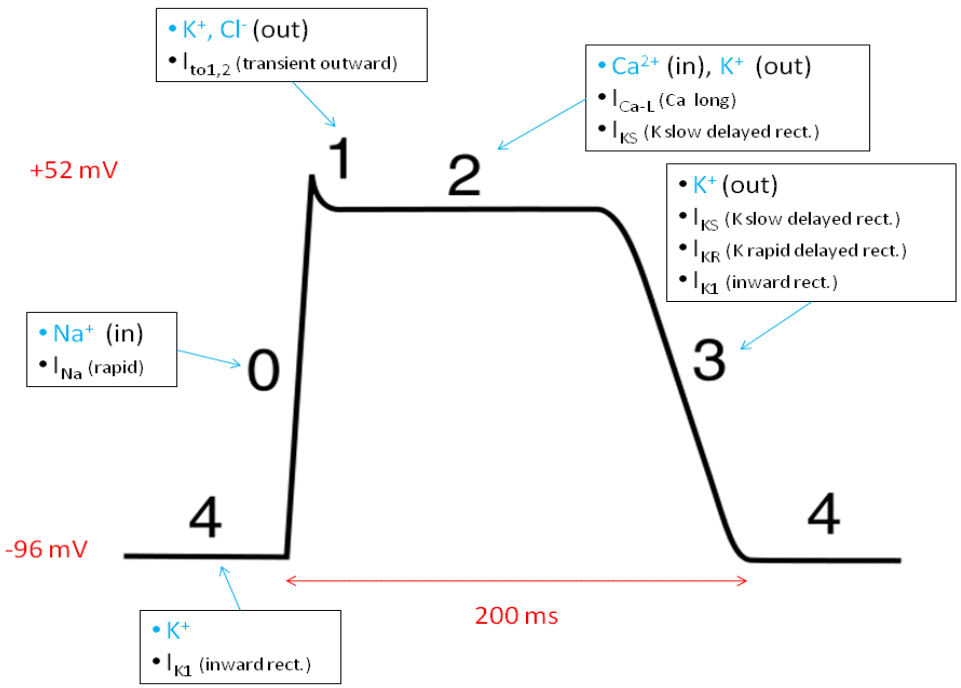


In this case the presence of infection, hypokalaemia, hypomagnesaemia and in particular the administration of QT prolonging drugs were all felt to have attributed to the development of TDP in a patient with previously normal ECG and QT interval.

Mechanism of TDP

The action potential of cardiac cells depends on transmembrane ionic movement involving several channels subtypes. Potassium plays a critical role in cardiac cell depolarisation and repolarisation and imbalances in extra/intracellular potassium are known to destabilise cardiac myocytes and predispose to arrhythmia. In particular two important subtypes of the delayed rectifier current, I_{Kr} (rapid) and I_{Ks} (slow) are known to play an essential role in phase 2 and 3 of ventricular repolarisation. (Figure 4) Drugs that prolong the QT interval do so by blockade of the rectifying potassium channels. In particular the I_{Kr} channel appears to be particularly susceptible to pharmacological blockade.(1,2,4,6) By blocking the $I_{K}r$ channel, phase 3 of repolarisation is prolonged evidenced by QT prolongation on the surface ECG. As the QT interval lengthens the ECG demonstrates abnormalities in the T and U wave. Early after depolarisations (EADs) can arise as a result of activation of inward depolarising currents due to the late entry of calcium through voltage gated calcium channels.

Figure 4: Cardiac Action Potential



The prolongation and variation in repolarisation amplifies spatial dispersion and acts as the principal substrate for arrhythmia provocation.(1) Combined with triggered activity arising from EADs this can lead to re-entry and the onset of TDP. The classical sequence of TDP onset has been described as slow-fast-slow. Typically a run of ventricular extrasystoles is followed by a compensatory pause terminated by a normal sinus beat. The QT interval of the sinus beat is markedly prolonged and when a critically timed ventricular extrasystole falls on the exaggerated T/U wave TDP is precipitated. (Figure 5)

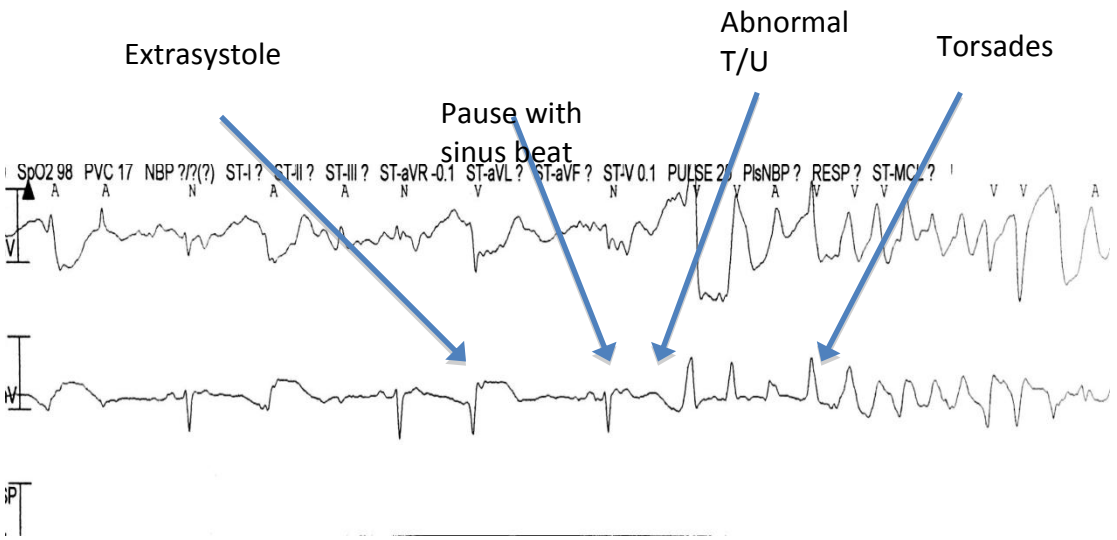


Figure 5: Rhythm strip indicating typical features prior to onset of TDP

Whilst TDP is normally self-terminating occasionally DC cardioversion is required due to haemodynamic compromise or degeneration into ventricular fibrillation.

Prevention and management of TDP

As described in our case it is often the combination of several factors that lead to the occurrence of TDP. By having an awareness and knowledge of these risk factors and limiting patient exposure to them it may be possible to reduce the risk of developing TDP. In patients suffering from electrolyte abnormalities it would be prudent to perform a baseline ECG and repeat this on a daily basis if the QT interval is prolonged. Electrolyte abnormalities

should be corrected and in particular it is recommended that potassium should be replaced aiming for a serum concentration between 4.5 - 5mmol/L. (2,6)

The list of QT prolonging drugs is extensive and includes many commonly used drugs such as antiarrhythmics, antibiotics, psychiatric drugs, anti-emetics and anti-histamines. Referring to national formularies and product literature may provide further insight into an individual drugs ability to prolong the QT interval. It would therefore be advisable to discontinue these drugs in patients with prolonged QT. Additionally it is important to recognise that a drugs ability to prolong the QT interval and lead to TDP may be unrelated to the dose used and the degree of QT prolongation.

Patients who develop TDP should have immediate direct current cardioversion performed if there is evidence of haemodynamic compromise. In those experiencing self-terminating episodes the initial treatment is the prompt removal of presumed precipitants as described above. In addition to potassium replacement it is recommended that patients experiencing TDP receive 1-2g of intravenous Magnesium Sulphate irrespective of the serum level. Whilst the mechanism of magnesium in this setting is not fully understood it is proposed that its beneficial effect comes from blockade of inward Sodium and Calcium currents.(6)

Neither potassium or magnesium administration will shorten the QT interval however they may stabilise the myocardium until the removal of the precipitant enables the reversal of the QT prolongation. Shortening of the QT interval may help suppress EAD's, reduce QT dispersion and therefore reduce the risk of TDP. This can be achieved through the intravenous administration of chronotropic agents such as isoprenaline aiming for a heart rate >100 bpm. An alternative strategy would be to consider insertion of a temporary transvenous pacing system again aiming for a rate >100bpm.(4,7)

If the QT interval shortens following removal of precipitants and the patient remains stable then no further strategies may be required. Occasionally it may be deemed appropriate to insert permanent pacing systems or cardioverter defibrillators if the risk of recurrence is deemed high. For example in the case of our patient the QT interval was slow to normalise, only occurring 10 days after correction of electrolyte abnormalities and removal of

offending agents. However due to the requirement for on-going chemotherapy and therefore the increased risk of infection and requirement for anti-emetic agents it was felt that a permanent pacing system would be beneficial. Due to a perceived life expectancy of less than one year we opted against the implantation of a cardioverter defibrillator. A base rate of 70bpm was set in DDD mode and due to the presence of frequent ventricular ectopics, bisoprolol was added to her medication regimen. No further arrhythmias were demonstrated following this or at 6 week and 3 month device interrogations.

Conclusion

As demonstrated by our case, acquired QT prolongation can occur as a result of individual factors or a combination of several precipitants. Awareness of the QT interval and avoidance of precipitating or exacerbating factors in the clinical setting may help to prevent the development of TDP. In particular, judicious use of drugs known to prolong the QT interval may help prevent this arrhythmia in at risk patients. In the event of QT prolongation the first step should involve conservative measures aimed at eliminating the precipitant. Daily monitoring of the QT interval and an awareness of the potential for variation are essential. Whilst TDP is often self-terminating, treatment may involve correction of serum potassium levels, administration of intravenous magnesium and in resistant cases administration of chronotropic agents or cardiac pacing.

References

1. Roden D M. A practical approach to Torsade de Pointes. *Clinical Cardiology*; 1997, 20 , 285-290
2. Yap Y G, Camm J A. Drug induced QT prolongation and Torsades de pointes. *Heart*; 2003, 89, 1363 – 1372
3. Kumar V, Sandeep K, Stancu M. Torsade de pointes induced by hypokalemia from Imipenem and Piperacillin. *Case Reports in Cardiology*; 2017.
4. Thomas S H L, Behr E R. Pharmacological treatment of acquired QT prolongation and torsades de pointes. *British Journal of Clinical Pharmacology*; 2015, 81(3), 420-427

5. Drew B J, Ackerman M J, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*, 2010, 121, 1047-1482
6. Tamargo J. Drug induced Torsade de Pointes: From molecular biology to bedside. *Japanese Journal of Pharmacology*; 2000, 83, 1-19
7. Li M, Ramos L G. Drug induced QT prolongation and torsades de pointes. *Pharmacovigilance Forum,* 2017, 42 (7), 473-477
8. Antzelevitch C, et al. Cellular and Ionic mechanisms underlying erythromycin induced long QT intervals and torsade de pointes. *JACC*, 1996, 28 (7), 1836-1848.
9. Viskin S. Idiopathic polymorphic ventricular tachycardia: a “benign disease” with a touch of bad luck? *Korean Circulation Journal*, 201, 47 (3), 299-306.