

### OVERVIEW OF THE ECG

The rhythm is irregular with multiple different QRS morphologies. The overall rate on this 10 second strip is 114bpm, but the wide QRS tachycardia has an average rate of 168 over 5 seconds. There are 2 complexes of normal width, preceded by P waves which are probably of sinus origin (upright in SII, inverted in aVR – P axis about +45°). The first 2 QRS complexes are followed by 2 wide premature complexes, a pause and then the irregular polymorphic wide QRS tachycardia, which terminates spontaneously.

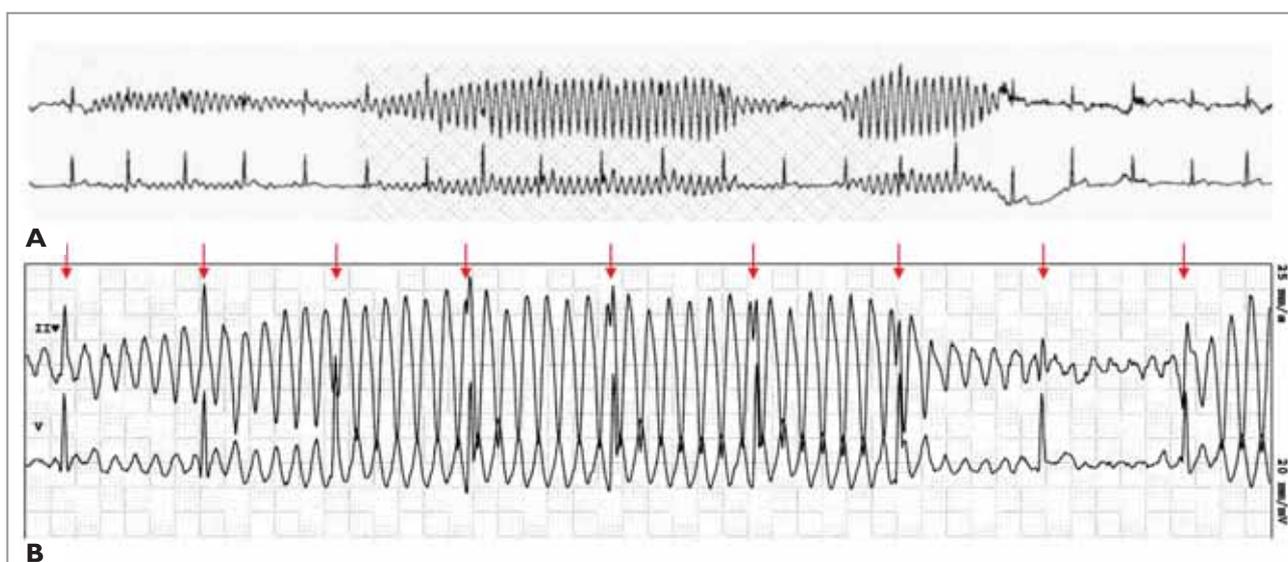
### MORE DETAILED ANALYSIS

When faced with a complex rhythm and multiple QRS morphologies, it is best to start with the most normal complexes, if any. The sinus beats seen in the limb leads are narrow (80ms) with a normal axis of +50° and no manifest abnormalities. The ST segments are down sloping and depressed in the inferior leads, elevated in aVR, and blend into the T waves. The QT interval is difficult to measure because of the T wave abnormality, but is at least 660ms. Correction for rate is not meaningful in this context but the QT is clearly markedly prolonged.

The QRS complexes of the wide QRS tachycardia are bizarre and variable. None is compatible with a pattern of right or left bundle branch block.

Could the apparent irregular wide QRS rhythm be an artefact due to seizure? The marked variation in morphology is suggestive. However, careful examination of the tracing does not reveal any evidence of normal QRS complexes marching through, which is the hallmark of an artefact (Figure 1).

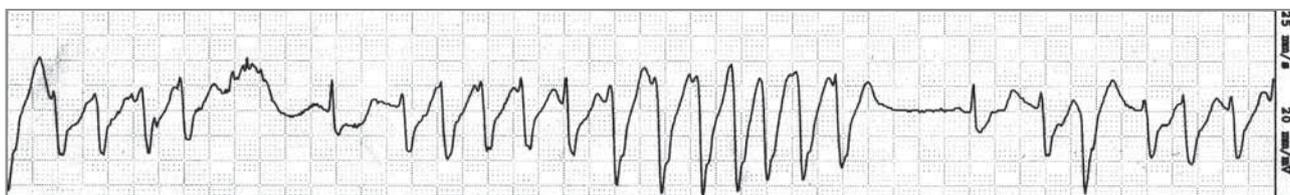
Pre-excited atrial fibrillation is a mechanism for a rapid, irregular wide QRS tachycardia with variable morphology. This is due to predominant conduction of atrial fibrillation via an accessory pathway with a short refractory period in a patient with Wolff-Parkinson-White syndrome (Figure 2). In this case, V1 varies from dominantly positive to dominantly negative within a few beats. For this to occur, at least 2 accessory pathways would have to be present, with conduction fusing between them. While multiple accessory pathways are common in WPW, the initial deflections in the first 3 beats in V4 - V6 are negative, indicating an origin in the region of the left ventricular apex. This excludes pre-excitation, in which all accessory pathways insert around the base of the heart around the AV ring. Finally, the onset of the tachycardia after a short-long sequence is not



**FIGURE 1:** Rhythm strips showing artefact: (A) 20 second strip; (B) 10 second strip at 25mm/sec. Note the normal QRS complexes in the artefact (arrows).



**FIGURE 2:** Irregular wide complex tachycardia with variable QRS morphologies characteristic of pre-excited atrial fibrillation. The variable QRS morphologies are due to varying degrees of fusion of conduction over the accessory pathway and AV node. There is a single narrow QRS complex because of conduction exclusively over the AV node and His Purkinje system with no pre-excitation over the accessory pathway.



**FIGURE 3:** Polymorphic VT secondary to acute myocardial infarction (Note: the QT interval is not obviously prolonged).



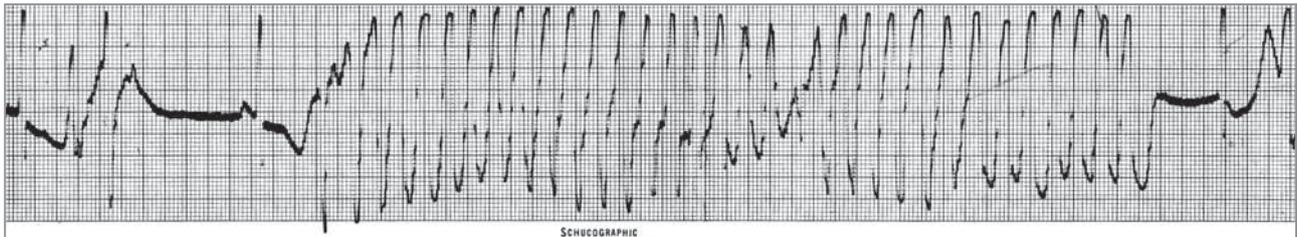
**FIGURE 4:** Bradycardia-induced prolongation of the QT interval can result in torsades de pointes triggered by a PVC after a short-long-short sequence.

typical of pre-excited AF, which usually is triggered by an episode of atrioventricular re-entry tachycardia, and tends to persist until it is terminated therapeutically.

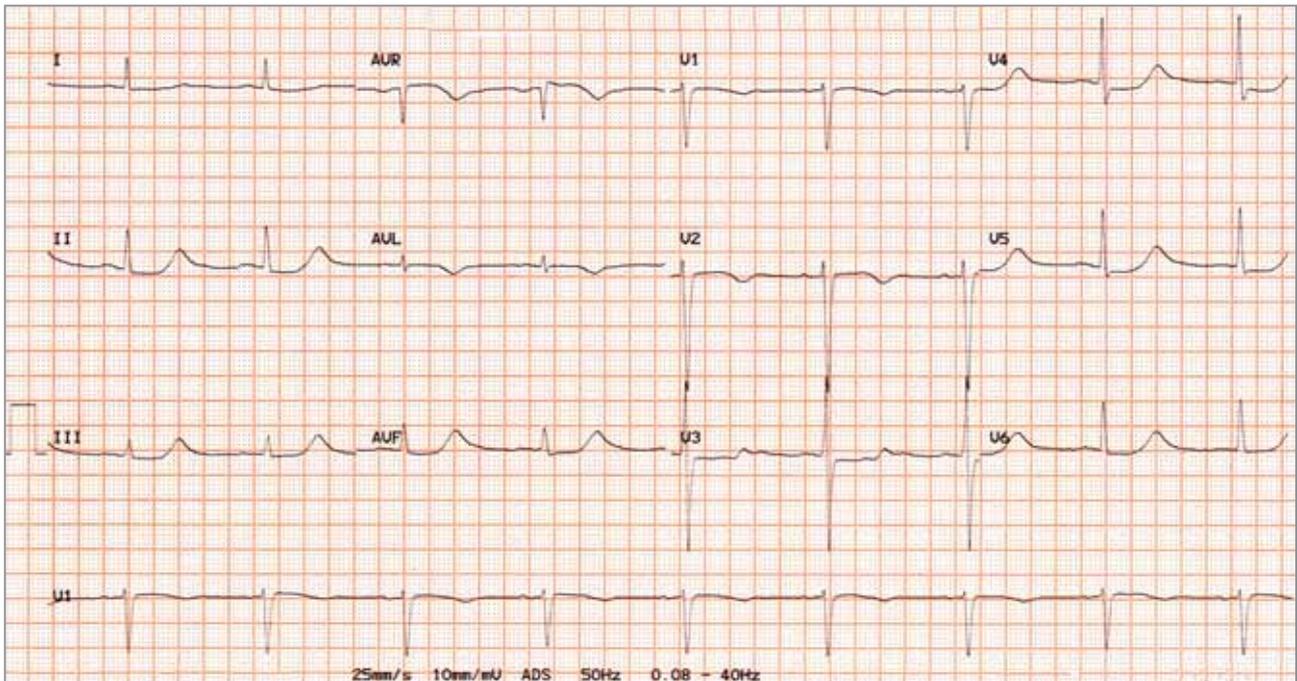
The slow onset of depolarisation in all the wide complexes indicates a ventricular origin. They are clearly polymorphic, so polymorphic ventricular tachycardia (VT) is a correct but incomplete description of this arrhythmia. The most common clinical setting for non-sustained polymorphic VT is acute myocardial infarction (Figure 3). While the rhythm in that condition may closely resemble this patient's ECG, including

the twisting pattern, it usually lacks the features which make the diagnosis of torsades de pointes more likely. These are:

- A markedly prolonged QT interval
- Onset after a short-long-short sequence, usually induced by a preceding premature ventricular complex. In this case, 2 PVCs after a sinus beat result in a pause. The following sinus beat is followed by another PVC at the end of the T wave, which triggers the run of torsades.



**FIGURE 5:** Torsades due to quinidine being used to treat atrial fibrillation – quinidine syncope.



**FIGURE 6:** ECG of the patient after resuscitation, confirming the very long QT interval.

**The correct answer is therefore (c): Torsades de pointes.**

#### COMMENT

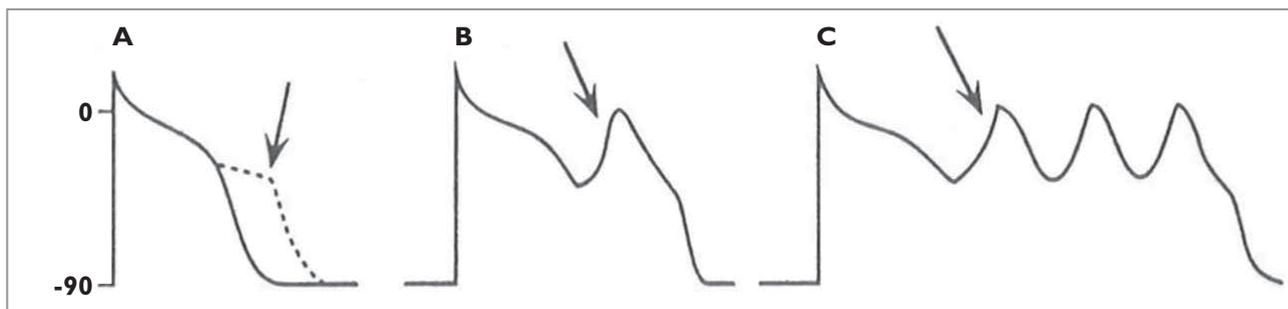
Torsades de pointes (TDP) is a term originally coined by Desserteine in 1966.<sup>(1)</sup> He described a number of cases based entirely on the pattern of a series of ventricular beats that appeared to twist around an axis – hence the “twisting of the points”. It has subsequently acquired a more specific connotation, in that it is linked to prolongation of ventricular depolarisation as expressed by a prolonged QT interval.

TDP induced by catecholamines is characteristic of the congenital long QT syndrome and is a cause of familial sudden cardiac death. It will not be discussed further here.

The most common form of TDP is related to bradycardia, e.g. complete heart block (Figure 4) or drug-induced QT pro-

longation (Figure 5). In the latter case, it typically follows a short-long-short sequence, as seen in this ECG strip.

This patient was being treated with sotalol for an unspecified arrhythmia. She now suffered from pancreatic cancer and was jaundiced, causing itching, for which an antihistamine was added. Her serum potassium was 2.7mmol/L from diuretic therapy. She was defibrillated on several occasions. The episodes of TDP stopped over the next 12 hours after sotalol and the antihistamine were withdrawn, an infusion of magnesium sulphate was given, and her serum potassium corrected. An ECG after resuscitation showed sinus bradycardia at 54bpm, normal QRS complexes, T wave inversion in aVL and V1 - V4, with minor ST depression (Figure 6). The QT was 640ms, QTcB 607 (upper limit of normal in a female is 450ms).<sup>(2)</sup>



**FIGURE 7:** IKr blockers prolong stage 3 of the action potential (A) Early after depolarisations (EADs) in stage 3 of the action potential (B) can generate further action potentials (C) if a threshold is reached that can precipitate ventricular fibrillation.

### DRUG-INDUCED QT PROLONGATION AND TORSADES POINTES

Drug-induced QT prolongation is now recognised as being extremely common.<sup>(3)</sup> The earliest description of quinidine syncope was in the 1920s,<sup>(4)</sup> but it was not until the 1970s that the problem of the pro-arrhythmic effects of antiarrhythmic drugs became increasingly recognised. This was followed by the realisation that the phenomenon was not confined to antiarrhythmics. The contribution of ancillary factors, such as hypokalaemia and drug combinations, which either both prolonged QT or interfered with metabolism and increased blood levels of the QT-prolonging drug, became clearer.

We published a series of patients from Johannesburg in 1984 in whom TDP was due to a combination of sotalol and a thiazide diuretic, which was being used to treat hypertension.<sup>(5)</sup> Sotalol is unique among beta blockers in prolonging the QT,<sup>(6)</sup> which accounts for some of its antiarrhythmic efficacy – but makes it more dangerous for other indications in which a pure beta blocker is appropriate. Despite this, it took several years before the combination (Sotazide™) was taken off the South African market.

The patient presented in this quiz had tolerated sotalol without ill effect until an antihistamine, also a known risk for TDP, was introduced for itch due to jaundice and the risk aggravated by a low serum potassium related to the diuretic.

### MECHANISM

The most common mechanism for drugs to prolong repolarisation and hence the QT is blockade of the potassium channel I<sub>Kr</sub>.<sup>(3)</sup> When of sufficient degree, early after depolarisations (EADs) tend to develop (Figure 7). These may manifest as premature ventricular complexes (PVCs). Because of different repolarisation characteristics between different layers of the myocardium, re-entry circuits may be set up, resulting in TDP, which may degenerate into ventricular fibrillation.

**TABLE I:** Risk factors for drug-induced torsades de pointes.<sup>(3)</sup>

- Female gender
- Hypokalaemia
- Bradycardia
- Recent conversion from atrial conversion with a QT prolonging drug
- Congestive heart failure
- Digitalis therapy
- High drug concentrations (except quinidine)
- Baseline QT prolongation
- Subclinical long QT syndrome
- Ion channel polymorphisms
- Severe hypomagnesaemia
- Hypocalcaemia

### RISK FACTORS (TABLE I)

Both individual susceptibility and external factors may play a part in the risk of developing TDP. Females after puberty have a reduced repolarisation reserve related to hormonal differences, as do males on anti-androgen therapy for prostate cancer. Subclinical genetic abnormalities of the potassium channel may play a part. Drug interactions are a frequent risk.

### DRUGS

The drugs involved are legion. IKr has been called a promiscuous channel. A full list can be found at <https://www.crediblemeds.org/index.php/login/dlcheck>. QT prolongation has become the single most common reason for a drug in development to be rejected.

Table II shows a partial list.

### PREVENTION AND TREATMENT

Primary prevention consists in avoiding QT-prolonging drugs if alternatives exist, especially in those at higher risk (Table I). If a QT-prolonging drug is indicated, at least a baseline ECG

**TABLE II:** Some of many drugs known to cause TDP.<sup>(7)</sup>

<b>Antiarrhythmics</b>	<b>Anticancer drugs</b>
• Quinidine	• Arsenic trioxide
• Sotalol	<b>Antimalarials</b>
• Dofetilene	• Chloroquine
• Amiodarone	• Hydroxychloroquine*
<b>Antibiotics</b>	• Halofantrine
• Moxifloxacin	<b>Antifungal</b>
• Erythromycin	• Fluconazole
• Azithromycin*	<b>Antiretroviral</b>
<b>Antidepressants</b>	• Lopinavir/ritonavir combination*
• Citalopram SSRI	<b>Anaesthetic</b>
<b>Antipsychotics</b>	• Propofol
• Haloperidol	<b>Calcium channel blocker</b>
• Thioridazine	• Beperidil
<b>Antiemetics</b>	<b>GI stimulant</b>
• Domperidone	• Cisapride
• Ondansetron	<b>Opioid</b>
<b>Antihistamines</b>	• Methadone
• Astemizole	

\*These drugs are being considered for treatment of COVID-19 and are currently undergoing randomised controlled trials.

should demonstrate a normal QTc and follow up ECGs are desirable. Avoid concomitant use of drugs which increase QT, as well as diuretics or laxatives that may lower serum potassium. Also avoid drugs that interfere with each other's metabolism. An example is the addition of ketoconazole, itself a prolonger of QT, to a drug which shares the CYP3A4 pathway for metabolism by the liver. For example, a combination of erythromycin with an antihistamine for an upper respiratory infection may trigger TDP.

Greater awareness among all prescribers would help.

Treatment consists in withdrawing offending drugs, administration of intravenous magnesium sulphate, and correction of low serum potassium. If this is insufficient, temporary overdrive atrial or ventricular pacing<sup>(8)</sup> will usually stop the runs of TDP. It is mandatory for bradycardia-induced TDP, especially complete heart block.

## LESSONS AND CONCLUSIONS

The list of drugs known to induce QT prolongation currently stands at 276.<sup>(7)</sup> A smaller number has been proven to cause TDP, but all carry some risk, particularly in combination or in patients at increased risk (Table I).

The risk of TDP may not be apparent in smaller trials, but larger population-based databases have revealed an increased

incidence of sudden cardiac death, which was previously lost in the noise of competing cause of death. Examples include small but significant increases in mortality in patients prescribed erythromycin as opposed to ampicillin for upper respiratory tract infections and in those receiving antipsychotic drugs.<sup>(9,10)</sup>

- Sotalol should only be used if safer alternatives are ineffective or inappropriate
- Avoid diuretics, combinations of QT-prolonging drugs and those which interfere with each other's metabolism
- Check for interactions between medications at [https://www.drugs.com/drug\\_interactions.html](https://www.drugs.com/drug_interactions.html)

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**Conflict of interest: none declared.**

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