Initiation and management of polymorphic ventricular tachycardia: history gone full circle

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This editorial refers to 'Polymorphic ventricular tachycardia, ischemic ventricular fibrillation and torsade de pointes: Importance of the QT and the coupling interval in the differential diagnosis', by R. Rosso *et al.*, on page xxxx.

'I do not imagine that electrocardiography is likely to find any very extensive use in the hospital. It can at most be of rare and occasional use to afford a record of some rare anomaly of cardiac action.' Augustis Desiré Waller (1856-1922).[1]

In the current era of molecular 'multi-omic' approaches, new and clinically important observations from a simple surface electrocardiogram are both refreshing and inspiring to the practicing cardiologist. Indeed, they stand in contradiction to arguably one of the biggest understatements in cardiology by Waller, who recorded the first human electrocardiogram.[1]

In this issue of *European Heart Journal*, Rosso and colleagues present new data to accurately distinguish several subtypes of polymorphic ventricular tachycardia (VT), which have important implications in the management of post myocardial infarction sudden cardiac arrest.[2] They describe specific electrocardiographic characteristics of the new polymorphic VT entity they originally identified in 2019**:** 'quinidine-responsive polymorphic VT' in patients with coronary artery disease in the absence of acute myocardial ischemia in order to enable appropriate use of this antiarrhythmic, as other agents are ineffective in these patients.[3] This paper provides occasion to review our current understanding of existing polymorphic VT subtypes.

In the past decades, several polymorphic VT entities have been recognized in the presence of structural, ischemic and primary electrical disorders. The most common and oldest described entity is primary ventricular fibrillation in the setting of acute myocardial ischemia, followed by the description of torsade de pointes (TdP) by Dessertenne in 1966,[4] and supplemented with short-coupled TdP[5] and polymorphic VTs in the primary electrical disorders over the past three decades. These entities can frequently be distinguished from one another by assessing the clinical characteristics of the patient (e.g., age, known underlying condition, family history), the baseline electrocardiogram, the initiation of the polymorphic VT, particularly whether or not the initiation is pause dependent, the coupling interval of the initiating ectopic beat, the initial rate, and the response to certain interventions (**Graphical abstract**).

In individuals without apparent structural heart disease or coronary artery disease, polymorphic VTs will often be caused by primary electrical disorders, idiopathic ventricular fibrillation, or acquired and reversible causes. In these patients, assessment of the QT interval and provocation tests to unmask primary electrical disorders that cannot be diagnosed on the resting electrocardiogram are vital. Patients

with congenital or acquired long QT syndrome (LQTS) are at risk for TdP - a polymorphic VT with several unique characteristics.[6] Importantly, the initiation of TdP is often, but certainly not always, pause-dependent.[7] In other conditions like Brugada syndrome, early repolarization syndrome, and short QT syndrome, the first beats of the polymorphic VTs are more rapid than in TdP and coupling intervals of the initiating ectopic beat are usually relatively short. Short-coupled TdP is, by definition, characterized by an ultra-short coupling interval of the initiating ectopic beat (often $\leq$320 ms).[5] Polymorphic VTs in the setting of catecholaminergic polymorphic VT and Andersen-Tawil syndrome may have the typical bidirectional morphology and display a longer coupling interval of the initiating ectopic beat.

Structural heart disease is most often associated with monomorphic VTs, but primary polymorphic VTs may occur.[8] In patients with coronary artery disease, primary ventricular fibrillation in the setting of acute myocardial ischemia is well known. As aforementioned, Viskin and colleagues recently reported on the entity of polymorphic VT in patients with coronary artery disease in the absence of acute myocardial ischemia which responded to quinidine therapy.[3] A key issue in identifying this population to prevent further electrical storms and sudden cardiac arrests is to elucidate indicative clinical features. In the present paper, they further evaluated the electrocardiographic characteristics of 87 patients with this entity, in particular by focusing on the QT interval. In 32 patients the QT interval was prolonged. However, when comparing the polymorphic VTs of these patients, which were termed 'pseudo-TdP', with 53 patients with true TdP in the context of drug-induced LQTS, some important differences were noted. Most importantly, the coupling interval of the initiating ectopic beat was shorter than 400 ms in pseudo-TdP and (much) longer than 400 ms in true TdP. In addition, the QT interval in patients with pseudo TdP was shorter, the mode of onset was less often pause-dependent, and the initial R-R intervals were shorter than in true TdP. Finally, patients with pseudo-TdP responded well to quinidine therapy, whereas quinidine is obviously detrimental in true TdP due to its QT-prolonging properties. Thus, in patients with pseudo-TdP, polymorphic VTs occur in the presence of a prolonged QT interval, but not due to a prolonged QT interval.

The incidence of these newly reported quinidine-responsive polymorphic VTs in patients with coronary artery disease is unknown as the data were not collected prospectively in a systematic manner to define the true denominator. However, one could speculate that this mechanism, and not the well recognised mechanisms of primary ventricular fibrillation or scar-related monomorphic VT degenerating into ventricular fibrillation, may underlie a certain proportion of cases of sudden cardiac arrest and sudden cardiac death in individuals with coronary artery disease.

The mechanisms by which polymorphic VTs occurs in the peri-infarct zone in the absence of ischemia are yet to be fully determined in humans, where most of the data comes from mapping studies of triggering ectopic beats arising from Purkinje fibres.[9] Animals studies in the canine infarcts have shown that post myocardial infarction subendocardial Purkinje fibres which survive in the infarct had reduced maximum diastolic potentials, action potential amplitudes, and maximum depolarisation velocities compared with normal subendocardial Purkinje fibres.[10] The action potential durations in these surviving fibres are extremely prolonged creating optimal conditions for re-entry. Indeed, some surviving fibres demonstrate spontaneous diastolic depolarisations. Hence, these fibres may act both as triggers and substrate for initiation and maintenance of polymorphic VT. Polymorphic VT may either arise from local wavefront activation changes during re-entry or from multiple ectopic foci akin to the situation in cathecholaminergic polymorphic VT ('ping pong' hypothesis)[11], where spontaneous triggered Purkinje firing may occur. Indeed, there are some parallels with another form of ectopic triggered ventricular fibrillation by moderator band ectopy.[12] In this situation triggered beats arise from moderator band Purkinje cells which have longer refractory periods than the surrounding myocardium leading to local re-entry and initiation of ventricular fibrillation. Currently, the only reliable treatment is to ablate the focus, which can be challenging.

The importance of classifying and recognizing the aforementioned polymorphic VT subtypes are the different responses to pharmacologic interventions (**Graphical abstract**). As Rosso and colleagues observed that only quinidine was effective in treating these specific polymorphic VTs in patients with coronary artery disease, its increasing inaccessibility due to worldwide production shortages is very concerning,[13] akin to the situation with mexilitine.[14] It is paradoxical that a 'torsadogenic' drug like quinidine can act as an antiarrhythmic in this context. Quinidine exerts its effects though a number of mechanisms, principally through blocking the fast sodium inward current (I_{Na}), but it also blocks the slowly inactivating sodium current, the slow inward calcium current (I_{Ca}), the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed potassium rectifier current, the inward rectifier potassium current (I_{K1}), the ATP-sensitive potassium channel (I_{KATP}), the transient outward potassium current (I_{to}), and can inhibit the Na+/K+-ATPase akin to digoxin. The mechanism that it is effective in these polymorphic VTs in patients with coronary artery disease remains unclear, but it may act by inhibiting calcium entry and sarcoplasmic reticulum calcium uptake to prevent calcium overload and triggered activity.[15] Ionic currents and ion-channel expression differ between Purkinje cells and ventricular myocytes, most notably those associated with calcium handling. Distinct proarrhythmic calcium-mediated mechanisms lead to ectopic afterdepolarizations of Purkinje cells with increased delayed afterdepolarisations seen in post myocardial infarction Purkinje cells.[14] The fact that quinidine, a 400 year old drug derived from quinine used by South American Indians to treat malaria, is uniquely effective is remarkable, as it is also the only agent known to be of value in the Brugada and early repolarization syndromes, possibly

operating through inhibiting the I_{to} current in these contexts. The I_{to} current is particularly expressed in the distal Purkinje cells, which could explain the specific action of quinidine in preventing the opportunity of localized reentry post myocardial infarction when Purkinje to myocardial coupling is impaired to create optimal conditions for re-entry.[16] The short cycle lengths of polymorphic VT would indicate the Purkinje network is at least a component of the circuit due to its three times faster conduction versus myocardium. It would be interesting to know if the quinidine actually reduced ventricular ectopy burden in this context to indicate if it was acting on the trigger or the substrate for polymorphic VT and ventricular fibrillation by suppressing the 'angry Purkinje' system, as Viskin would put it.[3]

In conclusion, Rosso and colleagues are to be congratulated that, even after decades of publications on ventricular tachyarrhythmias, they are still able to provide new important and clinically relevant insights into polymorphic VTs, simply by going back to the carefully curated series of electrocardiograms that they have collected over the years, hence re-establishing an approach using an historical simple investigation and ancient drug in the modern era.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Graphical abstract legend

Causes of polymorphic ventricular tachycardia (VT) and their treatment. Different types of polymorphic VTs based on the underlying substrate are shown, from polymorphic VTs with a short coupling interval of the initiating ectopic beat on the left to those with a relatively long coupling interval of the initiating ectopic beat on the right. Electrocardiographic examples are also shown. CPVT, catecholaminergic polymorphic ventricular tachycardia; CI, coupling interval; ER, early repolarization; LQTS, long QT syndrome; TdP, torsade de pointes.