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CLINICAL RESEARCH
Arrhythmias

Polymorphic ventricular tachycardia, ischaemic ventricular fibrillation, and torsade de pointes: importance of the QT and the coupling interval in the differential diagnosis

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Aims Distinctive types of polymorphic ventricular tachycardia (VT) respond differently to different forms of therapy. We therefore performed the present study to define the electrocardiographic characteristics of different forms of polymorphic VT.

Methods and results We studied 190 patients for whom the onset of 305 polymorphic VT events was available. The study group included 87 patients with coronary artery disease who had spontaneous polymorphic VT triggered by short-coupled extrasystoles in the absence of myocardial ischaemia. This group included 32 patients who had a long QT interval but nevertheless had their polymorphic VT triggered by ectopic beats with short coupling interval, a subcategory termed 'pseudo-torsade de pointes] (TdP). For comparison, we included 50 patients who had ventricular fibrillation (VF) during acute myocardial infarction ('ischaemic VF' group) and 53 patients with drug-induced TdP ('true TdP' group). The QT of patients with pseudo-TdP was (by definition) longer than that of patients with polymorphic VT and normal QT (QTc 491.4 ± 25.2 ms vs. 447.3 ± 55.6 ms, $P < 0.001$). However, their QT was significantly shorter than that of patients with true TdP (QTc 564.6 ± 75.6 ms, $P < 0.001$). Importantly, the coupling interval of the ectopic beat triggering the arrhythmia was just as short during pseudo-TdP as during polymorphic VT with normal QT (359.1 ± 38.1 ms vs. 356.6 ± 39.4 ms, $P = 0.467$) but was much shorter than during true TdP (581.2 ± 95.3 ms, $P < 0.001$).

Conclusions The coupling interval helps discriminate between polymorphic VT that occurs despite a long QT interval (pseudo-TdP) and polymorphic arrhythmias striking because of a long QT (true TdP).

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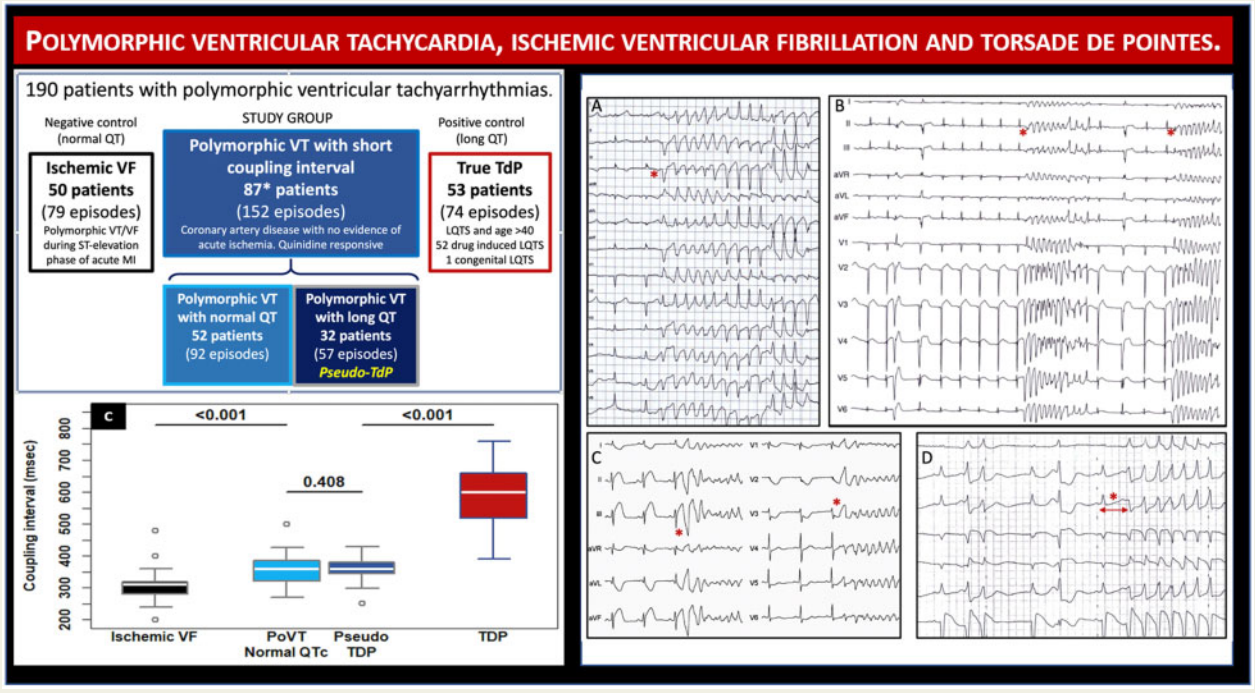
Graphical Abstract



Classification of patients with polymorphic ventricular tachyarrhythmias into three groups: a study group (with two subcategories) and two control groups used for comparison.

Keywords Polymorphic ventricular tachycardia • Ventricular fibrillation • Long QT • Torsade de pointes • Quinidine

Introduction

Polymorphic ventricular tachycardia (VT) is a malignant tachyarrhythmia with changing QRS pattern that will either terminate spontaneously (causing syncope if it lasts more than a few seconds) or will deteriorate to ventricular fibrillation (VF), causing cardiac arrest.[1] Defining the aetiology of polymorphic VT is of outmost importance because different forms of polymorphic VT respond to different forms of therapy. On the one hand, torsade de pointes (TdP), defined as the polymorphic VT caused by a long QT syndrome (LQTS), responds to beta-blocker therapy, intravenous magnesium, and cardiac pacing.[2] On the other hand, several forms of polymorphic VT not associated with QT prolongation, including the polymorphic VT of Brugada syndrome,[3,4] short QT syndrome,[5] and idiopathic VF,[6–10] are resistant to the above therapies but are highly responsive to quinidine.

Recently, we reported that arrhythmic storms caused by polymorphic VT in patients with coronary artery disease in the absence of acute myocardial ischaemia are also responsive to quinidine therapy when other antiarrhythmic drugs fail.[11,12] Some of our patients with quinidine-responsive polymorphic VT had a prolonged QT interval, either because they were recovering from a recent myocardial ischaemic insult,[13,14] or more commonly, because they had received amiodarone and failed to respond.[11,12] This observation mandates reassessment of the definition of TdP: distinguishing polymorphic VT occurring *because of* a long QT, from polymorphic VT occurring *in spite of* a long QT, is now imperative. For the former, 'true TdP', quinidine, a QT-prolonging medication, is obviously contraindicated. For the latter, 'pseudo-TdP', quinidine appears to be the drug of choice during arrhythmic storms.[11,12] We therefore conducted the present study to better define the electrocardiographic (ECG) characteristics of quinidine-responsive polymorphic VT—with and without QT prolongation—using the two following control groups as comparators: the first comparator was a 'negative-control' group with a well-defined form of polymorphic VT *not* related to QT prolongation. This group consisted of patients with 'ischaemic VF', defined as polymorphic VT/VF occurring during the ST-segment elevation phase of an acute myocardial infarction. The second comparator was a 'positive control' of bona fide LQTS, consisting of adult patients with LQTS.

Methods

The present study includes a total of 190 patients with spontaneous polymorphic ventricular tachyarrhythmias. A total of 305 arrhythmic episodes of polymorphic arrhythmias for which the mode of onset was available, were analysed in detail. Patients were classified into three different groups

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(*Figure 1*). The study group included 87 patients with coronary artery disease who developed spontaneous polymorphic VT in the absence of evident myocardial ischaemia. The clinical characteristics and response to quinidine therapy of the study group have been described in detail.[11,12] In brief, this group consists of patients with polymorphic VT initiated by ventricular extrasystoles displaying short coupling interval.[11,12,15,16,18] Several studies[15,16,18] confirm that these short-coupled ectopic beats originate from ischaemia-resistant Purkinje fibres[19] that endured in areas of myocardial scar.[16] We have used the term 'angry Purkinje syndrome' to describe this phenomenon.[20] Patients with this form of polymorphic VT characteristically develop arrhythmic storms that are refractory to beta-blockers, lidocaine, mexiletine, class 1C drugs, and amiodarone,[16] but are highly responsive to quinidine therapy.[11,12] In our own series, only 1 (2.1%) of 47 patients who received intravenous amiodarone responded to this drug, 45 (98%) of the 46 patients who received quinidine responded. This study group of patients with polymorphic VT related to coronary disease without evident acute myocardial ischaemia is referred throughout, for brevity, as 'the polymorphic VT group'. The arrhythmia onset was available for 152 arrhythmic episodes.

This polymorphic VT group of 87 patients was further stratified, based on the QT interval during sinus rhythm recorded shortly before the onset of arrhythmias, into two subgroups of polymorphic VT (*Figure 1*): (i) a subgroup of patients with short-coupled polymorphic VT and normal QT (referred here as the 'polymorphic VT with normal QT group'; *Figures 1 and 2A*); and (ii) the second subgroup consisted of otherwise similar patients who had a long QT interval but nevertheless had their polymorphic VT initiated by short-coupled ventricular extrasystoles (referred here as 'pseudo-TdP group'; *Figures 2B* and *3*). A total of 57 episodes of pseudo-TdP were studied. Long QT was defined as a QTc ≥450 ms for males and ≥460 ms for females (these values represent the 97th to 99th percentile of the normal QT).[21] For patients with wide QRS (defined as QRS ≥120 ms during sinus rhythm), we used a QRS-adjusted QTc.[22] This QRS-adjusted QTc represents the QTc that would be expected if these patients had narrow QRS. It is calculated by adding their measured JTc to an ideal QRS, where JTc = QTc—QRS.[22] The ideal QRS is 95 ms wide for men and 88 ms wide for women.[23]

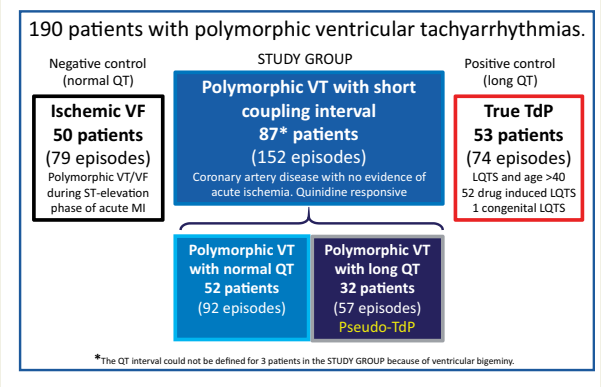

Figure 1 Classification of patients with polymorphic ventricular tachyarrhythmias into three groups: a study group (with two subcategories) and two control groups used for comparison. Note: Although all the three groups have polymorphic ventricular tachyarrhythmias, the term 'polymorphic ventricular tachycardia' is reserved for the study group, with a tachycardia that is well-defined by its clinical characteristics, mode of onset, and response to therapy.[11,12,15–17] LQTS, long QT syndrome; MI, myocardial infarction; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

The study group was compared with two control groups (*Figure 1* and *Graphical abstract*): (i) as negative-control group of patients with polymorphic VT that is clearly not related to QT prolongation, we included 50 patients with ischaemic VF. This ischaemic VF group consisted of patients presenting with acute myocardial infarction who developed VF at the time of obvious ST-segment elevation (*Figure 2C*). The arrhythmia onset was available for 79 ischaemic VF episodes. These patients underwent urgent cardiac catheterization confirming the ischaemic aetiology of the event; and (ii) as positive-control group of patients with arrhythmias clearly due to an LQTS (referred here as the 'true TdP' group), we included 53 adult patients (age ≥40 years) diagnosed and treated for LQTS for whom the onset of spontaneous TdP had been documented (*Figure 2D*). Patients with LQTS caused by severe bradyarrhythmias were excluded. All but one (a female patient with congenital LQTS presenting with TdP storm at the age of 60 years) had drug-induced TdP. A total of 74 episodes of true TdP were studied.

For all patients and controls, we analysed the following ECG parameters: (i) basic heart rate, QRS, QT, and QTc (QRS-adjusted QTc for patients with wide QRS); (ii) T-wave amplitude ratio (as measured by Kirchhof for patients with TdP),[24] denoting the ratio between the amplitude of the T wave immediately preceding the onset of arrhythmias to the amplitude of the T wave during undisturbed sinus rhythm in the same ECG trace; (iii) mode of onset of the arrhythmia [defined as either pause-dependent if the arrhythmia was immediately preceded by a pause (usually a post-extrasystolic pause creating a typical short–long–short sequence[25–27] or, less commonly, by a sudden increment in cycle length creating a long–short sequence)[26] or as non-pause-dependent[27] if it was not]; (iv) regardless of the mode of onset, we recorded the coupling interval of the ectopic beat triggering the VT and the cycle length of the subsequent initial four beats of VT. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. The retrospective collection of data and waiver of informed consent were approved by the Institutional Review Board (IRB) of the Tel Aviv Medical Center.

Statistics

All data are presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Continuous variables were compared using a Mann–Whitney *U*-test or a Kruskal–Wallis test as appropriate. Categorical variables were compared using a χ^2 test. A repeated measures mixed linear model was used to compare RR intervals of the four RR intervals between groups. A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study group consisted of 87 patients with coronary artery disease who developed spontaneous polymorphic VT in the absence of myocardial ischaemia. Of these patients, 24 (28%) were diagnosed or referred to us after our recent publications.[11,12] This study group consists of 36 patients who developed polymorphic VT within days of an acute myocardial infarction, 18 patients who developed this arrhythmia within days of a coronary revascularization procedure, and 33 patients with otherwise stable coronary artery disease who presented with out-of-hospital polymorphic VT. The ECG characteristics of these three subgroups were similar (Supplementary material

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online, *Table S1*) and these patients are presented together as the polymorphic VT study group.

Comparison of polymorphic ventricular tachycardia with ischaemic ventricular fibrillation

The polymorphic VT group and the ischaemic VF group were predominantly of male gender but patients with ischaemic VF presented at younger age (*Table 1*). Patients with ischaemic VF had shorter QT interval (*Figure 3A*). Of all arrhythmic episodes, only 8.9% of ischaemic VF episodes, but 31.6% of polymorphic VT episodes, were pause-dependent ($P < 0.001$). Regardless of the mode of onset, the coupling interval of the beat triggering the arrhythmia was short in both groups, but was significantly shorter during ischaemic VF (305 ± 53 vs. 358 ± 39 ms, $P < 0.001$). The arrhythmia was significantly faster during ischaemic VF (*Table 1* and *Figure 4D*).

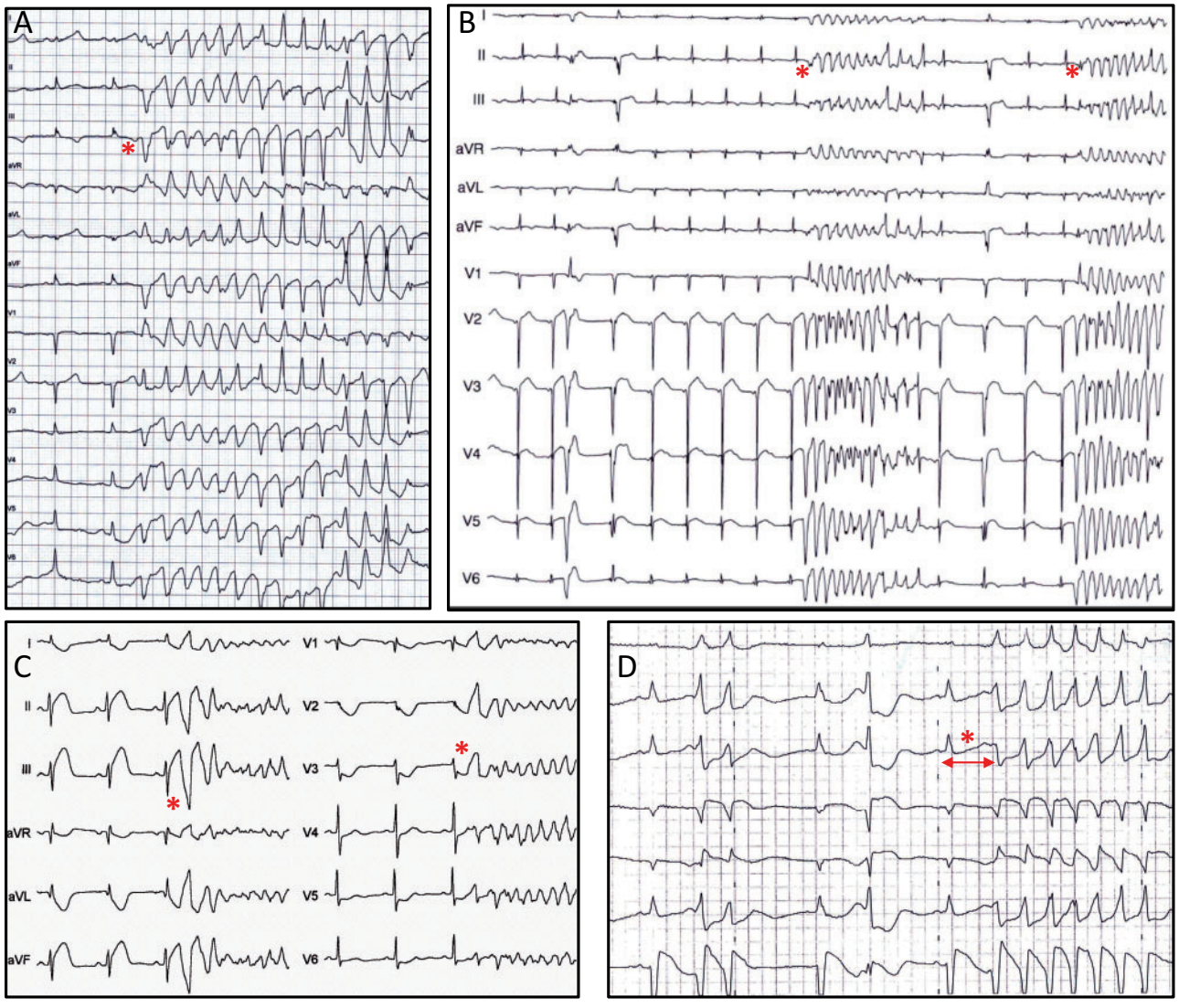

Figure 2 The four types of arrhythmias compared in the present study. (*A* and *B*) Episodes of short-coupled polymorphic ventricular tachycardia (with normal QT and with long QT, respectively) in patients with coronary disease but no apparent myocardial ischaemia. (*A*) This is from a 77-year-old male who developed a drug-refractory arrhythmic storm 4 days after coronary bypass surgery. Urgent catheterization showed that all grafts were patent. The QT is 367 ms and QTc 448 ms. He responded to quinidine therapy. (*B*) This is from a 51-year-old male recovering from an anterior myocardial infarction who developed an arrhythmic storm on Day 4 while receiving amiodarone for non-sustained ventricular tachycardia. This particular panel is shown at low paper speed (12.5 mm/s) so the high arrhythmia burden can be appreciated. Electrocardiographic recordings of the same patient are presented at 25 mm/s in *Figure 3A*. (*C*) An example of ischaemic ventricular fibrillation during ST-segment elevation of an acute inferior myocardial infarction. (*D*) A typical pause-dependent drug-induced torsade de pointes in a 62-year-old female treated with sotalol for atrial fibrillation. Her QTc is 592 ms. Note that the coupling interval (marked * in all panels) is short in polymorphic ventricular tachycardia (383 ms in *A*, 360 ms in *B*), is even shorter in ischaemic ventricular fibrillation (310 ms, *C*) but very long in torsade de pointes (650 ms in *D*). Also, note that the ventricular rate is fastest for ischaemic ventricular fibrillation, fast for polymorphic ventricular tachycardia, and relatively slow for torsade de pointes.

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Table 1 Comparison of ischaemic ventricular fibrillation with the short-coupled polymorphic ventricular tachycardia of patients with coronary disease without apparent ischaemia

	Ischaemic VF[a]	Polymorphic VT[b]	*P*-value
Number of patients	50	87	
Male gender	41 (82.0)	75 (86.2)	0.681
Age (years)	61.4±11.2	68.6±10.0	0.001
Basic RR	779.2±180.7	869.2±195.3	0.003
Basic QT	365.6±40.6	416.0±52.5	<0.001
QTc	417.1±27.4	451.0±43.7	<0.001
QTc narrow QRS only	417.6±27.5	445.8±35.9	<0.001
QTc adjusted for wide QRS[c]	417.1±27.4	443.6±43.3	<0.001
Long QT	3 (6.2)	32 (38.1)	<0.001
Arrhythmia onset			
Pause-dependent			0.008
All not pause-dependent	44 (88.0)	55 (63.2)	
All pause-dependent	3 (6.0)	17 (19.5)	
Both types	3 (6.0)	15 (17.2)	
RR of short cycle[d]	548.0±341.6	436.9±141.1	0.735
RR of long cycle[d]	860.0±299.1	1130.6±253.9	0.030
Coupling interval	305.4±52.8	357.8±38.5	<0.001
Mean RR of first beats of VT/VF	216.0±37.9	244.0±35.6	<0.001

All ECG values in milliseconds. All results presented as mean ± standard deviation or numbers and percentage.
ECG, electrocardiographic; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Ischaemic VF defined as polymorphic VT or VF at the time of presentation with ST-elevation myocardial infarction, before revascularization.
[b]Polymorphic VT refers to the well-defined phenotype of short-coupled polymorphic VT in patients with coronary disease without apparent acute myocardial ischaemia.[11,12]
[c]See text for definition.
[d]Short and long cycles immediately preceding pause-dependent events (entered only for pause-dependent events).

Comparison of polymorphic ventricular tachycardia with torsade de pointes, including comparison of pseudo-torsade with true torsade de pointes

In contrast to all other groups, female gender predominated in the group of drug-induced TdP (*Table 2*). Within the polymorphic VT group, 52 patients had normal QT interval. In three additional patients, the QT could not be accurately defined because all traces prior to the onset of polymorphic VT showed ventricular bigeminy. Finally, 32 patients with polymorphic VT had a long QT interval and are referred here as patients with pseudo-TdP (*Figure 1*). A total of 74 episodes of pseudo-TdP with documentation of the arrhythmia onset were available for review.

By definition, the QT of patients with pseudo-TdP was longer than that of patients with polymorphic VT and normal QT (QTc 491 ± 25 ms vs. 426 ± 33 ms, $P < 0.001$) (*Table 2* and *Figure 4*). Nevertheless, the coupling interval of the beat triggering pseudo-TdP (359 ± 38 ms) was just as short as the coupling interval triggering polymorphic VT with normal QT (358 ± 39 ms, $P = 0.4$).

The most important comparison is that of pseudo-TdP with true TdP (*Table 2*, *Figures 4B–D* and *5*). Although the QT was long in both groups, it was significantly longer in true TdP (QTc of 491 ± 25 ms for patients with pseudo-TdP vs QTc of 565 ± 76 ms for true TdP, $P < 0.001$). Nevertheless, there was significant overlap between the QTc of patients with pseudo-TdP and that of patients with true TdP. Specifically, 78% of patients with pseudo-TdP and 54% of patients with true TdP had a QTc within the range of overlap (QTc between 470 and 550 ms). On the other hand, the coupling interval provided good discrimination between pseudo-TdP and true TdP: only 2 (6%) patients with pseudo-TdP had a coupling interval longer than 400 ms. The first is a 75-year-old female patient who developed an arrhythmic storm (3 days after coronary bypass surgery) that failed to respond to intravenous lidocaine, magnesium, and amiodarone (*Figure 6*). The coupling interval of the ectopic beat triggering VT events ranged from 416 to 446 ms (*Figure 6B and C*). Her 12-lead ECG revealed that the ectopic beats had a narrow QRS (*Figure 6A*) with a coupling interval of 400 ms. She was treated with quinidine and had an immediate response. The second patient with pseudo-TdP and coupling interval >400 ms had two episodes of VF; one started with a coupling interval of 446 ms but the other one had a coupling interval of 390 ms. In contrast, the vast majority (94.3%) of patients with true TdP had arrhythmias starting with a coupling interval longer than 400 ms. The remaining 3 (5.7%) patients with true TdP had a coupling interval of 400 ms: two had drug-induced TdP (one male with a QTc of 495 ms from methadone and one female with a QTc of 519 ms from levofloxacin); the third patient has genotype-negative congenital LQTS who presented with recurrent implantable cardioverter-defibrillator shocks due to TdP refractory to beta-blockers. Based on recent reports,[28–30] she was treated with mexiletine with a good response.

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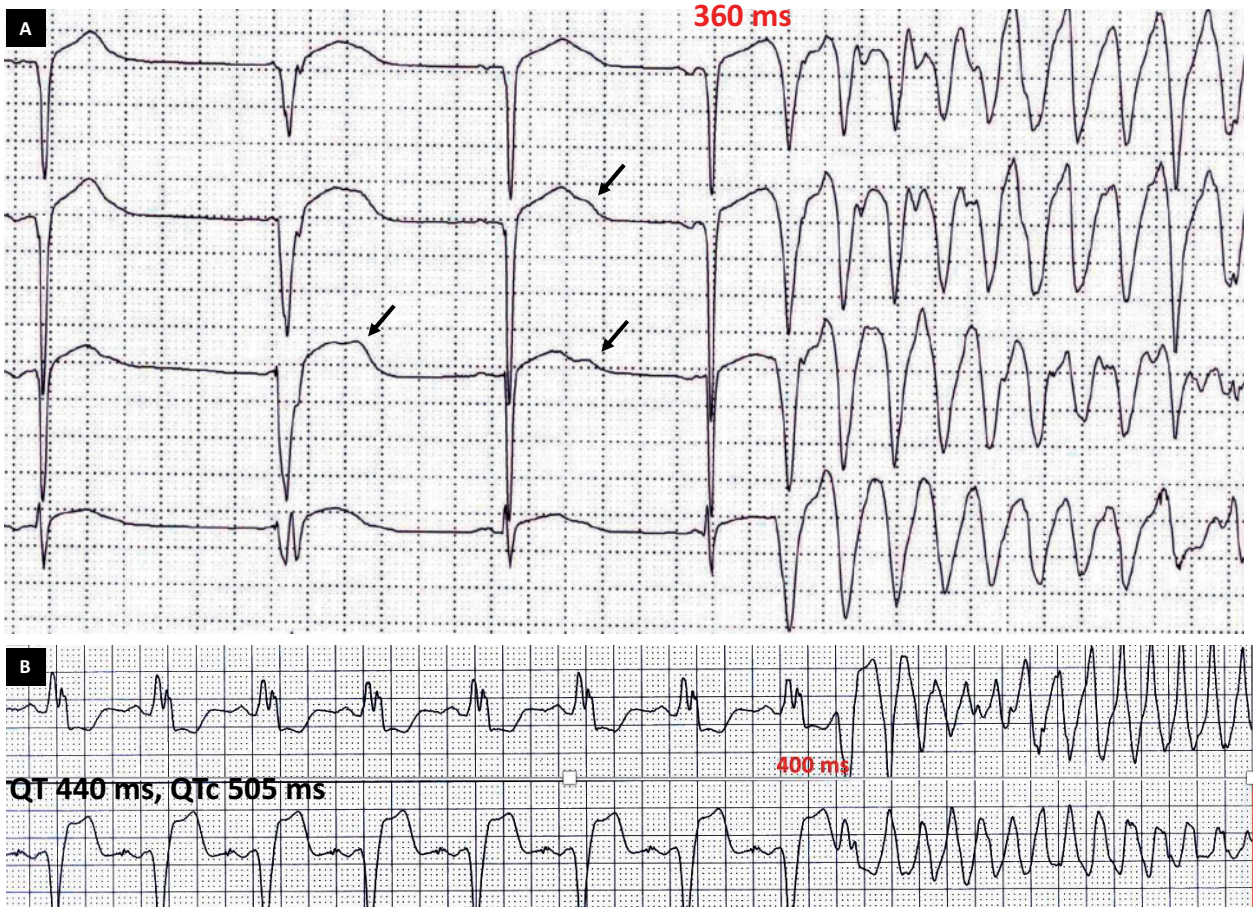

Figure 3 Two examples of pseudo-torsade de pointes. (*A*) This is from the same patient shown in *Figure 2B*. He developed an arrhythmic storm with frequent episodes of polymorphic ventricular tachycardia while receiving amiodarone. Note that his QT is not only very long (QTc 511 ms) but also has highly abnormal morphology with notched T waves (arrows). However, the coupling interval of the ventricular tachycardia is short (360 ms), demonstrating that the polymorphic ventricular tachycardia is occurring despite the long QT and not because of it. (*B*) This is from a 62-year-old male who has an implantable cardioverter-defibrillator and receives sotalol for monomorphic ventricular tachycardia. He presented with recurrent polymorphic ventricular tachycardia triggering numerous implantable cardioverter-defibrillator shocks (not shown). He was originally diagnosed with torsade de pointes because of a QTc of 505 ms while on sotalol and he was therefore treated with potassium and magnesium supplements while the atrial pacing rate of his device was increased to 80 b.p.m. These interventions failed to abort his arrhythmic storm and he received a total of 13 shocks. The relatively short coupling interval (400 ms) prompted initiation of quinidine with an immediate response. He has been free of arrhythmias for 5 years.

Regarding the mode of onset, 31.6% of pseudo-TdP events but 71.6% of true TdP episodes, were pause-dependent ($P < 0.001$). Regardless of their mode of onset, the ventricular rate during tachycardia, as assessed by RR intervals of the first four arrhythmia complexes of VT (excluding the coupling interval), was fastest during ischaemic VF (average heart rate of 278 b.p.m.), intermediate for polymorphic VT (245 b.p.m.), and was relatively slow for TdP (average of 183 b.p.m.) (*Figure 4D*).

Discussion

Distinctive types of polymorphic VT respond differently to different forms of therapy. In fact, interventions that are ineffective, or even contraindicated for one type, may be the treatment of choice for the other. We therefore compared the ECG characteristics of three forms of polymorphic VT that may strike in patients with organic heart disease: (i) polymorphic VT occurring in patients with coronary disease but without evident acute ischaemia; (ii) ischaemic VF, and (iii) TdP. Comparisons were made with emphasis on the QT interval and the coupling interval of the initiating beat of the tachyarrhythmia. Our results should prompt a paradigm shift in the way we diagnose TdP.

Comparison of polymorphic ventricular tachycardia with ischaemic ventricular fibrillation

As expected for patients with coronary disease, patients in both groups were predominantly of male gender. However, patients with

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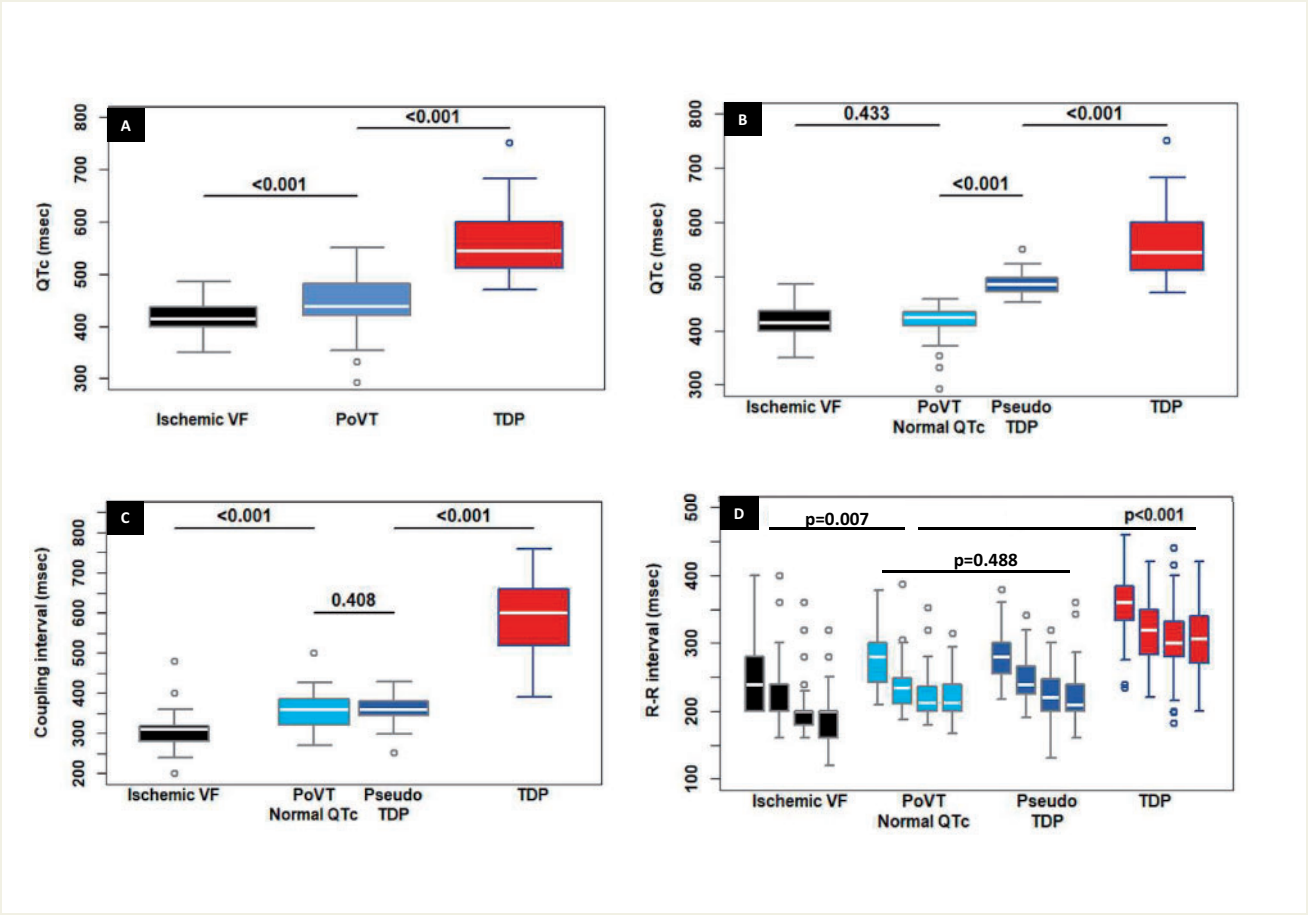

Figure 4 Boxplots of main electrocardiographic characteristics. In all panels, the coloured boxes represent the interquartile range (25th to 75th percentiles), with the white line representing the 50th percentile. The bars denote the range of values (excluding outliers, which appear as small circles). Values for ischaemic ventricular fibrillation appear in black, values for drug-induced torsade de pointes (TDP) in red, and values for polymorphic ventricular tachycardia appear in blue [light blue for polymorphic ventricular tachycardia with normal QT and dark blue for polymorphic ventricular tachycardia with long QT (pseudo-TDP)]. In (*A–C*), *P*-values are shown for comparisons between two adjacent boxplots. In (*D*), *P*-values are for group comparison in reference to polymorphic ventricular tachycardia with normal QTc. For within-group comparisons, *P*-values are <0.001 for all groups. Note that the QT is shortest for ischaemic ventricular fibrillation, intermediate for polymorphic ventricular tachycardia and longest for true TDP (*A*). By definition, the QT interval of patients with pseudo-TDP was longer than of the remaining patients with polymorphic ventricular tachycardia (dark blue vs. light blue in *B*) but shorter than the QT of true TDP (*B*). Despite their longer QT interval, episodes of pseudo-TDP had a coupling interval that was as short as that of polymorphic ventricular tachycardia with normal QT and significantly shorter than the coupling interval of true TDP (*C*). Once the tachycardia started, the ventricular rate was fastest during ischaemic ventricular fibrillation. The ventricular rate during polymorphic ventricular tachycardia was also fast (regardless of the QT interval) and significantly faster that the ventricular rate during true TDP (*D*).

ischaemic VF were, on average, 7 years younger. This finding is consistent with previous studies suggesting that younger age at the time of myocardial infarction is associated with increased risk of primary VF.[31] Also, the QT interval prior to the onset of the arrhythmia was shorter for patients with ischaemic VF, a finding consistent with *in vitro* studies showing significant shortening of the action potential during simulated ischaemia.[32] Finally, in both polymorphic VT and ischaemic VF, the initiating beat of the arrhythmia had a short coupling interval, yet shorter during ischaemic VF. In fact, the coupling interval at the time of ischaemic VF initiation is among the shortest recorded,[33] comparable only to that of idiopathic VF, an arrhythmia notorious for an ultra-short coupling interval.[34]

The mechanism of the short-coupled polymorphic VT patients with coronary disease has been well described in humans. Patients with this type of arrhythmia characteristically develop arrhythmic storms that are resistant to conventional antiarrhythmic therapy.[11,12,16] Consequently, several studies have provided detailed information collected during endocardial mapping at the time of ablation procedures.[15–17] Recording of the sites of onset of spontaneous arrhythmias in humans demonstrates that ectopic beats originating from the Purkinje fibres, surviving within areas of

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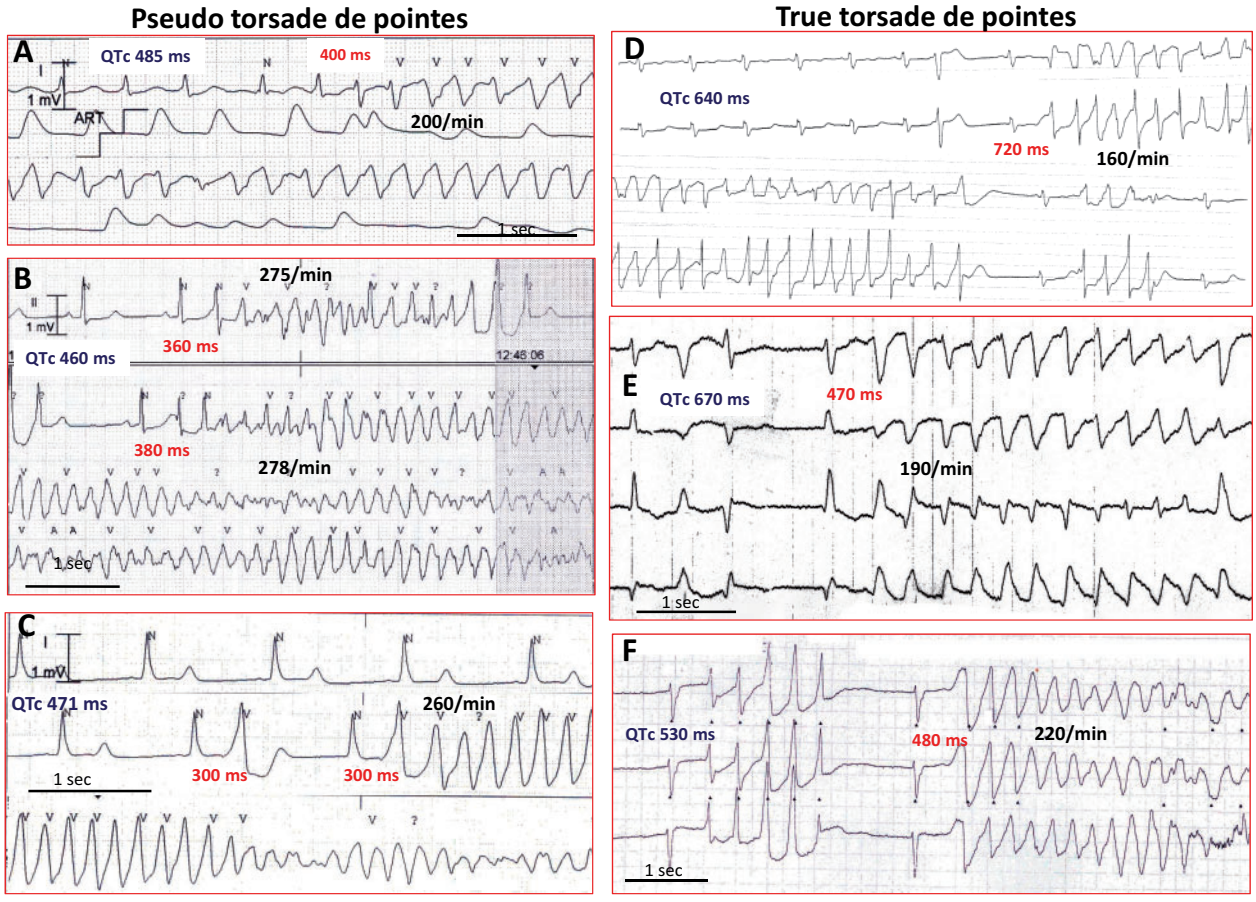

Figure 5 Examples of polymorphic ventricular tachycardia with long QT interval and short coupling interval pseudo-torsade de pointes and true torsade de pointes. In all traces, the QTc is shown in blue, the coupling interval of the beat starting the ventricular tachycardia in read, and the average ventricular rate during the first five beats of ventricular tachycardia in black. The QTc for traces showing ventricular bigeminy was measured in additional traces from the patient (now shown). (*A–C*) Pseudo-torsade de pointes in three different male patients (age 62–65 years) who developed arrhythmic storm within days of a myocardial infarction (*A*) or after coronary bypass surgery. (*D–F*) Drug-induced torsade de pointes in female patients (age 60–82 years). The torsade de pointes was caused by amitriptyline, high-dose trimethoprim/sulfamethoxazole, and citalopram (*D*, *E*, and *F*, respectively). All patients with torsade de pointes had concomitant hypokalaemia. Note that the QT interval is prolonged in all six cases shown here, but it is appreciably longer in the three patients with true torsade de pointes (*D–F*). Furthermore, the coupling interval (in red) and the ventricular cycle length during tachycardia (in black) are shorter for patients with pseudo-torsade de pointes.

myocardial scar, initiate these recurrent arrhythmias.[15–17] On the other hand, data on the mode of onset of ischaemic VF are available only from animal studies and *in vitro* preparations with simulated ischaemia.[35] Phase 2 re-entry (from non-ischaemic areas to ischaemic zones with abbreviated action potential) has been proposed to explain the mechanism of the ultra-short coupling during ischaemic VF.[36]

Comparison of polymorphic ventricular tachycardia and torsade de pointes

Polymorphic VT with normal QT is easily distinguishable from TdP. Thus, the comparison of interest if that of pseudo-TdP with true TdP. In agreement with previous studies,[37,38] the TdP group, which consisted almost exclusively of patients with drug-induced TdP, was predominantly of female gender. Both the pseudo-TdP and the true TdP groups had a long QT interval, but the QT was appreciably longer in the TdP group. The QT of patients with true TdP in our study (QTc 565 ± 76 ms) is consistent with the observation that the risk of TdP, among patients with LQTS, rises significantly as the QTc prolongs above 500 ms. In fact, other studies report even longer QT intervals, at the time of TdP, for patients with congenital or drug-induced LQTS (QTc of 589 ± 85 and 594 ± 84 ms, respectively).[25,26] Nevertheless, significant overlap existed between the QTc of our pseudo-TdP and true TdP groups (*Figure 4B*). On the other hand, the coupling interval of the beat initiating the tachycardia provided good distinction between pseudo and true TdP, with a value of 400 ms providing excellent discrimination. Since patients in both groups tend to

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Table 2 Comparison of the short-coupled polymorphic ventricular tachycardia of patients with coronary disease without apparent ischaemia [including polymorphic ventricular tachycardia with normal QT and polymorphic ventricular tachycardia with long QT (pseudo-torsade de pointes)] with true torsade de pointes

	PVT[a]		True TdP	PVT-normal-QT vs. pseudo-TdP	Pseudo-TdP vs. true TdP
	PVT-normal QT	Pseudo-TdP			
Number of patients	52	32	53		
Male gender	44 (84.6)	28 (87.5)	22 (41.5)	0.963	<0.001
Age (years)	70.1±10.3	66.5±9.6	66.4±13.2	0.092	0.814
Basic RR	886.5±193.4	841.6±201.3	954.3±229.8	0.236	0.012
Basic QT	396.8±40.2	447.3±55.6	549.0±109.3	<0.001	<0.001
QTc	426.1±32.6	491.4±25.2	564.6±75.6	<0.001	<0.001
QTc narrow QRS only	421.7±20.3	484.1±16.1	558.3±64.6	<0.001	<0.001
QTc adjusted (wide QRS)	416.8±29.5	487.1±20.9	561.9±74.7	<0.001	<0.001
Long QT	0	32 (100)	51 (100)	<0.001	—
T-peak to T-end	89.63±29.68	88.57±34.16	153.03±-41.87	0.444	<0.001
Arrhythmia onset					
Pause-dependent				0.965	<0.001
All not pause-dependent	34 (65.4)	20 (62.5)	17 (32.1)		
All pause-dependent	9 (17.3)	6 (18.8)	33 (62.3)		
Both types	9 (17.3)	6 (18.8)	3 (5.7)		
RR of short cycle	418.2±100.7	481.2±211.5	626.2±203.2	0.440	0.002
RR of long cycle	1138.1±272.7	1117.7±229.9	1249.8±295.7	0.796	0.185
Coupling interval	356.6±39.4	359.9±37.7	599.7±172.8	0.405	<0.001
Mean RR (first beats of VT)	239.1±31.8	246.6±32.3	327.8±59.2	0.185	<0.001

All ECG values in milliseconds. All results presented as mean ± standard deviation or numbers and percentage.
ECG, electrocardiographic; PVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; TdP, torsade de pointes.
[a]For 3 of the 87 patients with PVT, we could not accurately determine the QT interval because all ECG trace recordings during sinus rhythm preceding the arrhythmia showed ventricular bigeminy.

have recurrent arrhythmias; shorter (or longer) coupling intervals, observed in other events, are expected to facilitate the distinction. Interestingly, the ventricular rate during VT differed between groups, it was fastest for ischaemic VF and slowest for TdP. The long refractory period associated with action potential prolongation probably serves as a rate-limiting factor in TdP.

Limitations

This is a retrospective analysis of mostly a single-centre study experience. Its main limitation is the absence of a gold standard to define pseudo-TdP. One could argue that patients with pseudo-TdP have, in fact, true TdP with shorter QT interval and shorter coupling interval. However, the phenotype of polymorphic VT in the absence of apparent myocardial ischaemia, including the short coupling interval of ectopics triggering polymorphic VT, has been well-defined in numerous studies.[11,12,15–17] The fact that quinidine is highly effective in suppressing this arrhythmic phenomenon strongly argues against a diagnosis of TdP for these patients. As a reminder, the diagnosis of TdP has always been a clinical diagnosis, and appropriate therapy is delivered despite the absence of a gold standard for that diagnosis as well.

The second important limitation relates to the limited number of patients in the different categories. It is possible that as new patients are recognized, the coupling interval cut-off value that best distinguishes pseudo-TdP from true TdP will be better defined. Furthermore, since the TdP groups consisted almost entirely of patients with drug-induced TdP, the majority of events of true TdP were pause-dependent. Our findings should not be extrapolated to (the far less common) tachycardia-induced form of true TdP seen in some forms of congenital LQTS.[27]

Clinical implications

The diagnosis of TdP should not be given to patients with polymorphic VT who have a prolonged QT interval and develop polymorphic VT. Instead, this diagnosis should be reserved only for patients who develop the arrhythmia in the setting of an LQTS. This distinction is not simply semantic. Making the distinction between polymorphic VT that is caused by a long QT (as manifestation of a congenital or acquired LQTS) and a polymorphic VT occurring despite QT prolongation has important therapeutic implications. Quinidine, a QT-prolonging medication that is clearly contraindicated for TdP, is the drug of choice for polymorphic VT, including pseudo-TdP.[11,12]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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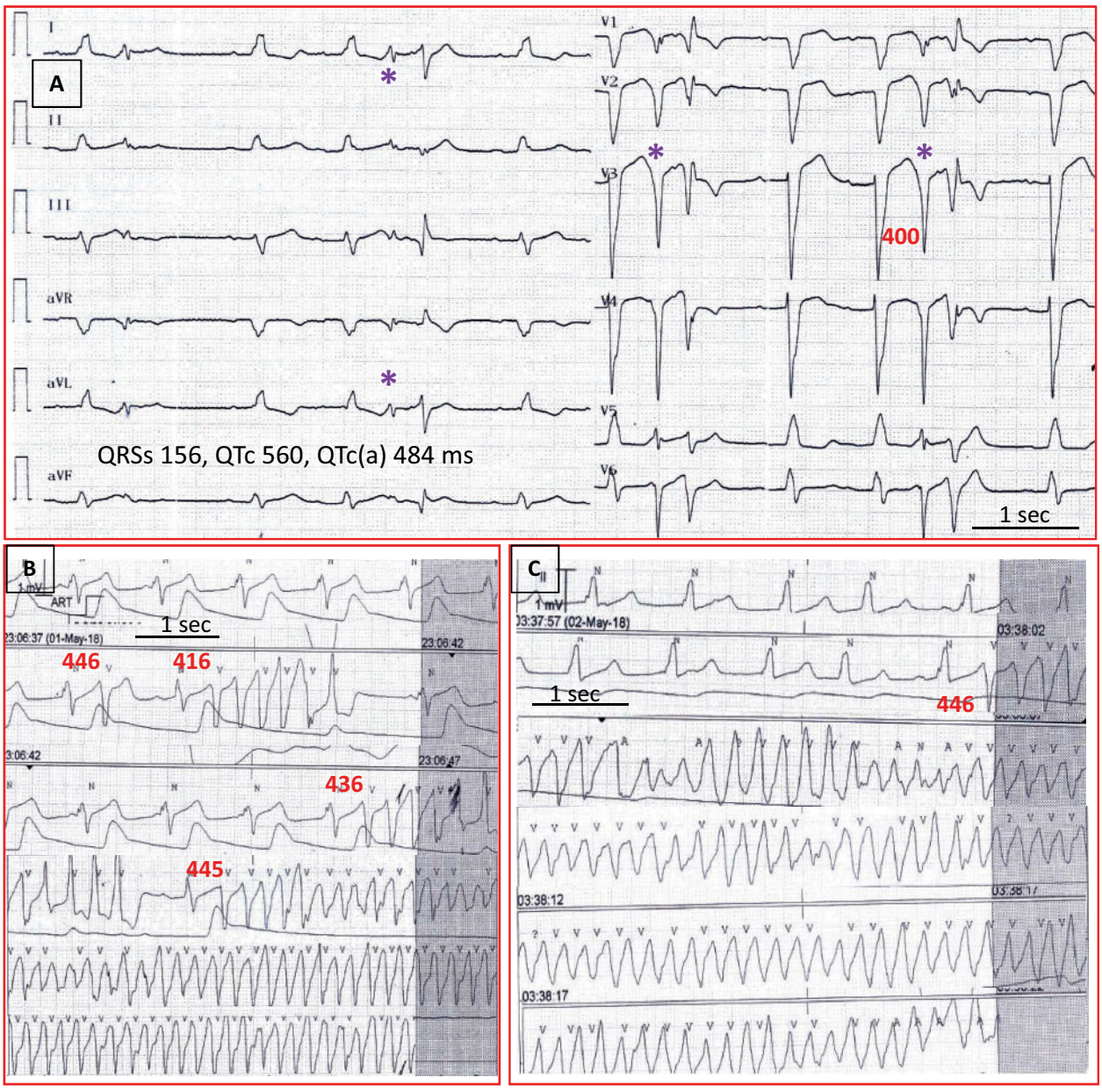

Figure 6 Electrocardiograms of a patient with pseudo-torsade de pointes with relatively long coupling interval. This 75-year-old female developed an arrhythmic storm 5 days after coronary bypass surgery. She has left bundle branch block with a QRS of 156 ms and a QTc of 560 ms (measured before the onset of ventricular bigeminy). The JTc is 404 ms and her adjusted QTc 484 ms (see text). She had multiple ventricular fibrillation episodes requiring defibrillation and failed to respond to intravenous lidocaine, magnesium, and amiodarone. Urgent catheterization showed a known critical lesion in the left anterior descending and a significant stenosis at the anastomosis of an arterial graft to the distal left anterior descending. The left anterior descending underwent dilatation and stenting. However, she continued to have recurrent ventricular fibrillation and ultimately was treated with quinidine with immediate response. Note that the coupling interval during different ventricular tachycardia episodes ranged from 416 to 446 ms (*B* and *C*). Importantly, her 12-lead electrocardiographic recording shows ectopic beats with a relatively narrow QRS (*). In fact, the ectopic beats (marked with the sign * in *A*) have a QRS width of 99 ms, which is narrower than the QRS during sinus rhythm and have a coupling interval of 400 ms, revealing the true nature of her arrhythmia: pseudo-torsade de pointes.

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Data availabilty

Data will be availabe upon request and IRB approval.

Conflict of interest: none declared.

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