Circulation

IN DEPTH

Polymorphic Ventricular Tachycardia

Terminology, Mechanism, Diagnosis, and Emergency Therapy

Sami Viskin, MD; Ehud Chorin, MD; Dana Viskin, MD; Aviram Hochstadt, MD; Arie Lorin Schwartz, MD; Raphael Rosso, MD

ABSTRACT: Polymorphic ventricular tachyarrhythmias are highly lethal arrhythmias. Several types of polymorphic ventricular tachycardia have similar electrocardiographic characteristics but have different modes of therapy. In fact, medications considered the treatment of choice for one form of polymorphic ventricular tachycardia, are contraindicated for the other. Yet confusion about terminology, and thus diagnosis and therapy, continues. We present an in-depth review of the different forms of polymorphic ventricular tachycardia and propose a practical step-by-step approach for distinguishing these malignant arrhythmias.

Key Words: Brugada syndrome ■ quinidine ■ tachycardia, ventricular ■ torsade de pointes ■ ventricular fibrillation

Polymorphic ventricular tachycardia (VT) is a malignant ventricular 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. Defining the etiology of polymorphic VT is of utmost importance because different types of arrhythmias with similar electrocardiographic characteristics respond to different forms of therapy. Furthermore, polymorphic VT often leads to arrhythmic storms, with clusters of VF episodes repeatedly requiring DC shocks for defibrillation. In such scenarios, medications that are life saving for one form of polymorphic VT may be contraindicated for the other. We present a contemporaneous classification of polymorphic VT and propose a practical step-by-step approach for distinguishing these malignant arrhythmias (Figure 1).

STEP 1: IS THE ARRHYTHMIA RELATED TO A LONG QT SYNDROME?

Polymorphic VT Caused by Long QT Syndromes

Torsade de Pointes

Terminology

Torsade de pointes ("twisting of the points" in French), was first coined by Dessertenne to describe the polymorphic VT that results from the long QT syndrome (LQTS) caused by complete atrioventricular block.[1] The original description referred to a tachyarrhythmia with "progressive changes in morphology, amplitude, and polarity of the QRS complexes, whose peaks twist around the isoelectric baseline." As narrated elsewhere,[2] Dessertenne did not recognize, at the time, the causal association between the long QT and the arrhythmia he was describing. Nevertheless, "torsade de pointes" was soon adopted for all forms of LQTS-related tachyarrhythmias.[2] Importantly, when recorded in multiple ECG leads, all forms of polymorphic VT may have this "twisting of the points" contour in some leads. Because LQTS-related arrhythmias have specific modes of therapy (see Emergency Therapy section), it is important to reserve "torsade de pointes" for arrhythmias *caused* by an LQTS.

Mechanism

The LQTS occurs when inborn (genetic) or developed (acquired) malfunctions of dedicated ion channels located in the myocardial cell membrane lead to reduced repolarizing currents via potassium channels or excessive depolarizing late-sodium currents.[3] The resulting delay in repolarization postpones the inactivation of calcium channels, and the resulting excessive inflow of calcium contributes to the formation of early afterdepolarizations (EADs). These EADs, which appear on the surface ECG as pathological,

Correspondence to: Sami Viskin, MD, Department of Cardiology, Tel Aviv Sourasky Medical Center, Weizman 6, Tel Aviv, Israel 64239. Email samiviskin@gmail.com
For Sources of Funding and Disclosures, see page 836.

Circulation is available at www.ahajournals.org/journal/circ

Nonstandard Abbreviations And Acronyms

CPVT	catecholaminergic polymorphic ventricular tachycardia
EAD	early afterdepolarization
ECG	echocardiogram
LQTS	long QT syndrome
RVOT	right ventricular outflow tract
SQTS	short QT syndrome
VF	ventricular fibrillation
VT	ventricular tachycardia

notched T-waves, may reach a threshold amplitude that triggers ventricular arrhythmias (Figure 2). Some regions of the ventricle in the deep subendocardium are more likely to show prolonged repolarization and EADs.[4,5] The resulting heterogeneity of repolarization permits the development of reentrant arrhythmias once triggered by EADs.

Diagnosis

The correct diagnosis of torsade de pointes is based on the following: (1) the likelihood that one of the congenital or acquired forms of long QT syndrome is present; (2) the QT interval during sinus rhythm is prolonged; and (3) the arrhythmia has a characteristic mode of onset. Specifically, the list of potential causes of long QT syndrome should be considered (Table)[3,6–15] and the probabilistic nature of the calculated rate-corrected QTc interval should be appreciated from evidence-based calculators (https://www.qtcalculator.org),[16] while keeping in mind that most patients with torsade de pointes have a QTc ≥500 ms at the time of arrhythmia documentation. The onset of torsade de pointes is determined by 2 fundamental characteristics: (1) the first beat of the tachyarrhythmia denotes an early depolarization reaching trigger potential at the late phase of the prolonged action potential[3] (consequently, the coupling interval [the time-interval between the last sinus complex, just before arrhythmia initiation and the first arrhythmia beat] is always long [>450 ms[17] or ≥500 ms[18] in different studies]); and (2) the abnormal QT fails to accommodate to sudden heart rate changes[19,20] (consequently, torsade de pointes starts during sinus rate acceleration [tachycardia-dependent torsade[17]] or, more commonly, during heart rate deceleration [pause-dependent torsade[21–23]]). Tachycardia-dependent torsade occurs mainly in infants and patients with type I congenital LQTS,[17] but may occur in drug-induced LQTS (although rare). Failure of the action potential to accommodate to an accelerating sinus rate characteristically leads to T-wave alternans, a well-known sign of imminent torsade de pointes (Figure 2C). Pause-dependent torsade de pointes is more common: it is the predominant form in adults with type 2 and 3 congenital LQTS[17,21] and is in the vast majority of cases with acquired forms of LQTS.[3] Here, a sudden

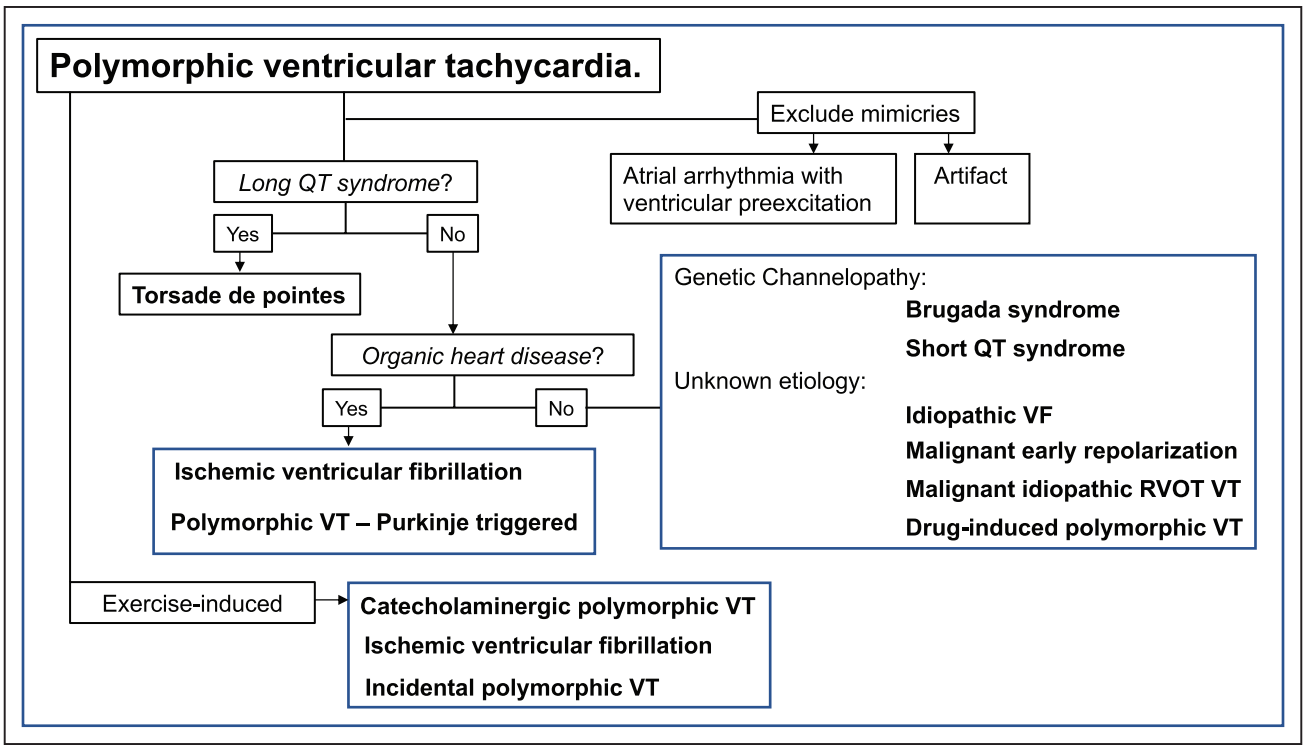

Figure 1. Approach to the patient with polymorphic VT.
After excluding mimicries of polymorphic VT, the first question is whether the patient has a long QT syndrome (not merely a long QT interval [see section on "pseudo–torsade de pointes"]); the second question is whether the patient has organic heart disease. Polymorphic VT recorded during exercise represents a different category. RVOT indicates right ventricular outflow tract; VF, ventricular fibrillation; and VT, ventricular tachycardia.

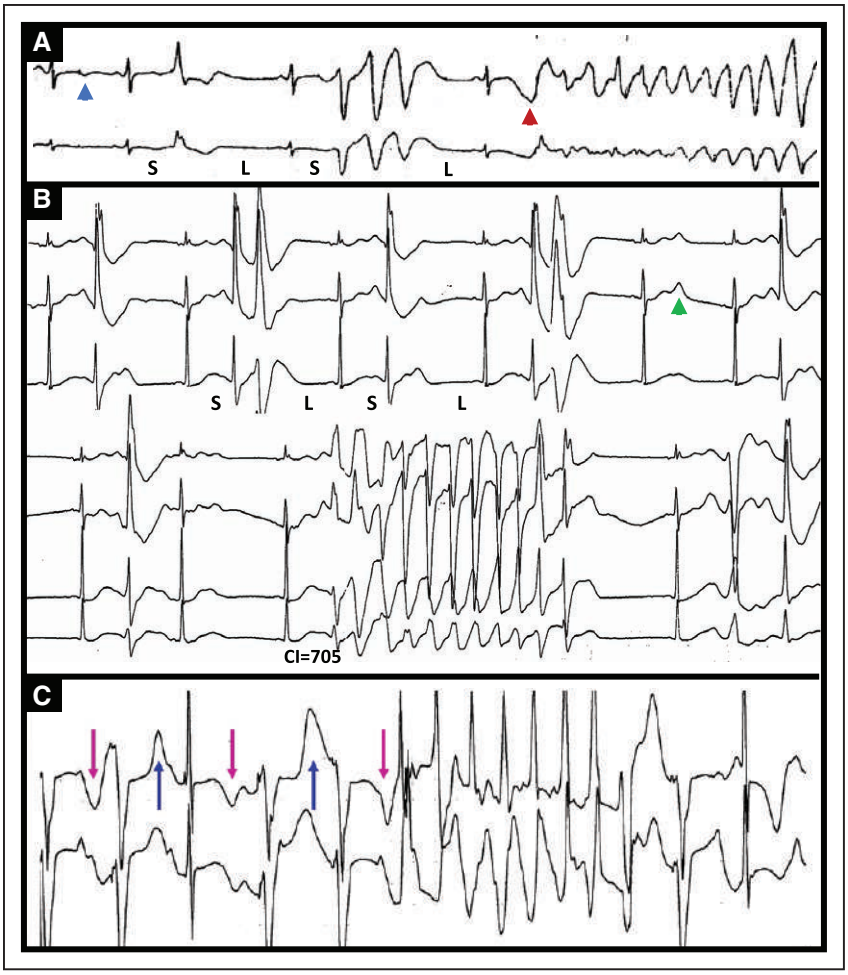

Figure 2. Pause-dependent and tachycardia-dependent torsade de pointes.
A and **B**, Pause-dependent torsade de pointes. Note the short-long-short sequence created by extrasystoles and their postextrasystolic pause (annotated S-L-S), preceding torsade de pointes. Comparison of the baseline QT (blue arrowhead) and the postpause QT interval (red arrowhead) in **A** clearly demonstrates the maladaptation of the QT interval to sudden decrease in heart rate secondary to the postextrasystolic pause. **B**, Drug-induced long QT syndrome from methadone and erythromycin; the abnormal (notched) T-waves reflect early depolarizations (green arrowhead). The coupling interval of the beat initiating torsade de pointes is long (coupling interval, 705 ms [marked CI=705] in panel B). **C**, Tachycardia-induced torsade in an infant with congenital long QT syndrome. Note the macroscopic T-wave alternans (arrows of different colors) caused by the maladaptation of the QT interval to the accelerating heart rate immediately preceding torsade de pointes.

heart rate slowing because of a sinus pause or, more commonly, a postextrasystolic pause, leads to augmentation of the EAD amplitude, which manifests in the ECG as postpause excessive augmentation of the T-wave amplitude, often leading to giant and bizarre T-waves[24] (Figure 2A). A vicious cycle, where each pause triggers new extrasystoles, creates a distinctive ECG pattern referred to as the "short-long-short sequence"[22] that ultimately culminates in torsade de pointes (Figure 2A and 2B).

Emergency Treatment

The emergency therapy of torsade de pointes includes discontinuation of any QT-prolonging medications and raising potassium serum levels to high-normal levels.[11] Sedation with intravenous midazolam is advised because any stress-induced rise in sympathetic tone is arrhythmogenic.

Intravenous magnesium, administered as slow intravenous bolus injection of 2 g magnesium sulfate, suppresses the onset of torsade.[25] The effects of magnesium are often transient, so intravenous magnesium is essentially a first-aid agent until additional therapeutic measures are instituted. It may be repeated as long as hypermagnesemia (in patients with impaired renal function) is avoided. Considering that magnesium suppresses EADs by blocking calcium inflow, more potent calcium channel blockers, like verapamil, have been proposed.[26,27]

The late-sodium current is arrhythmogenic in the LQTS.[28] Accordingly, mexiletine, a specific late-sodium current blocker,[29] is effective in suppressing torsade de pointes in both congenital[30,31] and acquired[32] forms of LQTS. Considering that lidocaine is often the first drug used to treat *any* ventricular arrhythmia, surprisingly little is known about its efficacy in torsade de pointes. Lidocaine blocks late-sodium current in vitro,[33] but at concentrations that would probably require supratherapeutic doses. In a small case series, it was usually given in conjunction with magnesium, precluding objective interpreta-

Table. The Long QT Syndromes

Congenital long QT syndrome[3]
Drug-induced long QT syndrome[6]
Bradycardia-induced long QT syndrome[7]
Posttachycardia long QT syndrome[9]
Postinfarction (or Takotsubo) long QT syndrome[10]
Hypokalemia (and metabolic abnormalities)[11]
Hypogonadism[15]
Food-induced long QT syndrome[12–14]

tion of the results. Lidocaine failure in patients ultimately responding to magnesium has been reported.

During arrhythmic storms, it is crucial to review the mode of onset of all arrhythmic events. Tachycardia-dependent torsade de pointes is best treated with high doses of β-blockers (and left cardiac sympathetic blockade if β-blockers fail). On the other hand, shortening the pauses that facilitate pause-dependent torsade with either cardiac pacing or isoproterenol is antiarrhythmic. The basic heart rate should be increased to the minimal rate that prevents pause-dependent torsade de pointes, taking into account that excessive heart rate acceleration may provoke tachycardia-induced torsade. Once all pauses are prevented by effective cardiac pacing, β-blockers can be safely used also for pause-dependent torsade de pointes.

STEP #2: ARRHYTHMIAS NOT RELATED TO AN LQTS: DOES THE PATIENT HAVE ORGANIC HEART DISEASE?

Polymorphic VT Without QT Prolongation

Polymorphic VT in the Absence of Organic Heart Disease

This category includes patients with genetic disorders (short QT and Brugada syndromes), and diseases of unknown etiology (idiopathic VF with or without early repolarization). These entities share important characteristics, including a tendency to develop arrhythmic storms (with recurrent polymorphic VT triggered by ectopic beats displaying a *short* coupling interval), which respond to quinidine therapy when other antiarrhythmic drugs fail.[34]

In addition, patients with the common and benign idiopathic monomorphic VT from the right ventricular outflow tract ([RVOT] RVOT-VT), rarely develop malignant polymorphic VT.[35–37] Finally, intriguing proarrhythmic effects of the antibiotic azithromycin may rarely lead to polymorphic VT.[38]

Genetic Channelopathies Leading to Polymorphic VT

Brugada Syndrome

Terminology

Brugada syndrome was originally described as "a distinct clinical and electrocardiographic syndrome of right bundle-branch block, persistent ST-segment elevation, and sudden death (Figure 3A)."[39] Interestingly, none of these 3 characteristics are universally present. First, it is not clear if the right bundle-branch block pattern represents a true block of conduction in the right bundle in all patients. Appearance of complete right bundle-branch block may actually hide the diagnostic pattern of ST-segment elevation.[40] Second, the ST-segment elevation, in those who have it, is not present at all times and is therefore not truly persistent.[41] Finally, although patients with this entity are at increased risk of VF, the majority of patients seen nowadays are asymptomatic when diagnosed and many remain free of arrhythmias during follow-up periods that now reach 20 years.[42]

Mechanism

Brugada syndrome is a genetic disorder. Monogenic inheritance attributable to disease-causing mutations in the SCN5A (sodium voltage-gated channel α subunit 5) sodium channel is found in about 20% of cases.[43] For the rest, oligogenic inheritance is suggested by genome-wide association studies showing that genetic variants in different genes (like SCN10A and HEY2), which are not pathogenic enough to cause disease when present in isolation, increase the likelihood of Brugada syndrome when present in combination.[44,45]

It is a matter of debate if the polymorphic VT of Brugada syndrome is caused by delayed conduction causing disorganized reentry, or if it is attributable to the abbreviation of the action potential in the right ventricular outflow, causing abnormal dispersion of repolarization ultimately generating phase 2 reentry.[46] Probably, both mechanisms take place to different degrees in different patients.[47]

Diagnosis

The typical patient with symptomatic Brugada syndrome is an adult male who develops cardiac arrest at rest, often while asleep, and often as a presenting symptom.[48] The classic arrhythmia in Brugada syndrome is a polymorphic VT triggered by an ectopic beat that has a short coupling interval, but not as short as in idiopathic VF. Recordings of spontaneous arrhythmias are mostly from intracardiac recordings in implanted defibrillators (Figure 3B). Therefore, information of the site of origin of spontaneous polymorphic VT in Brugada syndrome is limited. It is presumed to be the RVOT, but anecdotal cases show that this is not invariably the case (Figure 3C).

Among patients with ST-segment elevation in the precordial leads shortly after cardiac arrest, the obvious differential diagnosis is ischemic VF attributable to an anterior infarction or isolated right ventricular infarction.[49] The absence of reciprocal ST depression favors the diagnosis of Brugada over ischemic VF and, over time, the development of Q-waves will tell these 2 conditions apart. When in doubt, urgent coronary angiography is indicated because ischemic VF is more common and responsive to revascularization. ST-segment elevation may also be caused by repeated DC shocks during resuscitation; but this is a transient phenomenon.[50]

The absence of ST-segment elevation after resuscitation from cardiac arrest does *not* exclude Brugada syndrome because a surge in sympathetic tone during resuscitation may diminish ST-segment elevation.[51] In

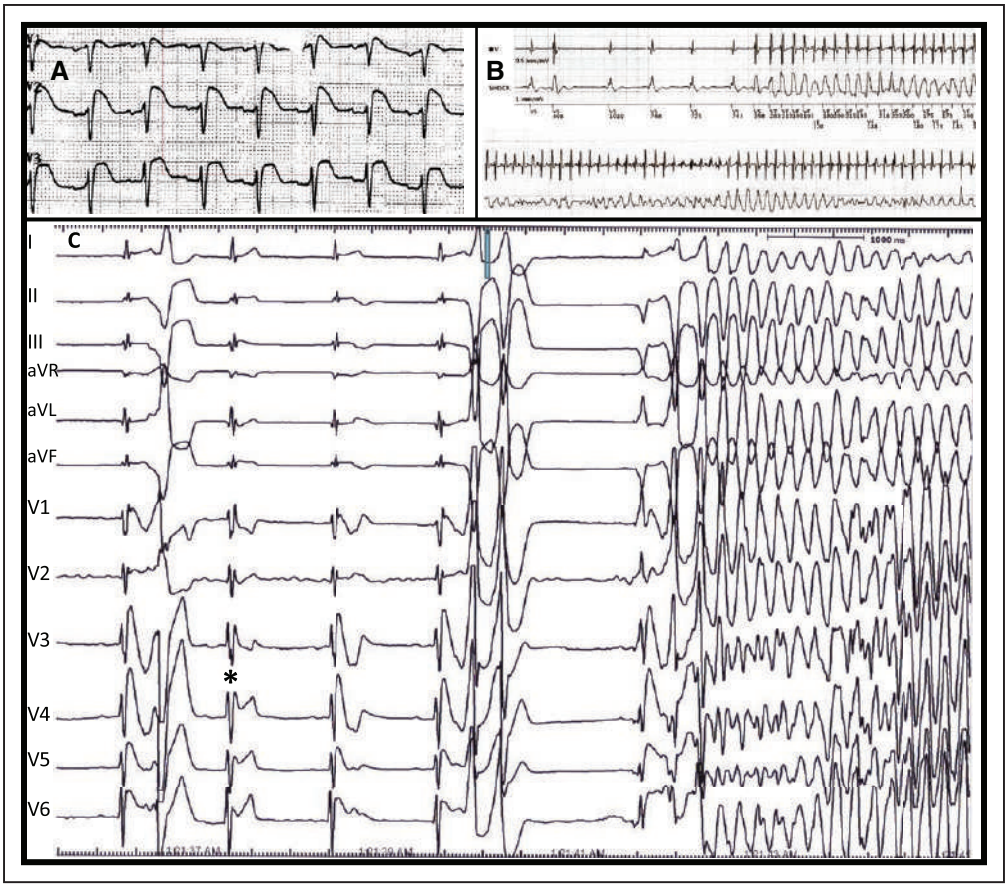

Figure 3. Polymorphic ventricular tachycardia in Brugada syndrome.
A, Typical type I Brugada pattern (only leads V1–V3 are shown). **B**, Representative event of spontaneous polymorphic ventricular tachycardia deteriorating to ventricular fibrillation as recorded by an implanted defibrillator (stored bipolar and shock-lead electrograms of the event). Note the relatively short coupling interval of the beat initiating the polymorphic ventricular tachycardia (coupling interval, 398 ms). **C**, Arrhythmic storm in a young patient with Brugada syndrome. The precordial leads (V1–V6) are placed in the 2nd and 3rd intercostal space rather than the nominal position. The arrhythmias are pause-dependent. The initiating beat has a superior axis, indicating that the site of origin is within the inferior aspect of the right ventricle rather than the expected right ventricular outflow origin. Note that the type I Brugada pattern disappears after short cycles, indicated in this figure by an asterisk (*).

fact, 1 out of 3 patients presenting with cardiac arrest eventually diagnosed with Brugada syndrome, do not have ST elevation at the time of presentation.[48] When circumstantial evidence suggests Brugada syndrome and the diagnostic ECG is not observed, 12-lead Holter with the precordial leads placed at higher costal interspace,[52] or a sodium channel blocker test (with ajmaline, flecainide, pilsicainide, or procainamide)[52,53] may unravel the typical Brugada ECG. One should keep in mind, however, that provocation tests with sodium channel blockers may result in false-positive diagnoses,[53–55] and may provoke life-threatening arrhythmias, although rare.[56]

Emergency Therapy

Case series document that VF storms in Brugada syndrome fail to respond to conventional antiarrhythmic drugs but respond to intravenous isoproterenol and/or oral quinidine. These drugs restore the homogeneity of repolarization by increasing calcium current (isoproterenol) or blocking the transient outward potassium current ([I_{To}] quinidine). Although randomized studies have not been performed, the evidence is compelling enough to recommend isoproterenol and quinidine as first line of therapy for arrhythmic storms in Brugada syndrome.[57,58] Quinidine is not available in all countries.[59,60] It is important to assure that hospitals, particularly arrhythmia referral centers, keep quinidine supplies on stock because this medication is lifesaving during arrhythmic storms. Intravenous quinidine is available for the treatment of malaria and may be used for VF storms.[61] Cilostazol and bepridil have been used in quinidine-intolerant patients.[57] Importantly, radiofrequency ablation of the arrhythmic substrate (identified as areas of abnormal, fractionated potentials) on the right ventricular outflow, using percutaneous epicardial approach, is effective for patients with recurrent VF events.[62]

Short QT Syndrome

Terminology

Short QT syndrome (SQTS) is a genetic disease. Although initially called "idiopathic short QT interval,"[63] the familial nature of the disease was evident from the initial

reports.[63,64] The more prevalent genetic mutations cause malfunction of the same repolarizing ion channels that cause the LQTS: loss-of-function in the I_{Kr} or I_{Ks} potassium channels ("rapid" and "slow" components of the delayed rectifier potassium current, respectively) cause prolongation of the action potential (LQTS), whereas gain-of-function of these channels causes QT shortening in SQTS. Mutations in the genes CACNA1C (calcium voltage-gated channel subunit α-1C) or CACNB2b (calcium channel voltage-dependent subunit β-2) cause a mixed phenotype of Brugada and SQTS.[65]

Mechanism

Genetic mutations causing SQTS result in excessive shortening of the action potential in some myocardial areas more than in others. The resulting increased transmural dispersion of repolarization is as proarrhythmic in SQTS as it is in LQTS.[5,65,66] Cellular models of SQTS that replicate the arrhythmogenic substrate caused by dispersion of repolarization still require external triggers, in the form of electric stimulation, to initiate VF.[65,67] Calcium-spark oscillations, which are prevalent in Purkinje fibers, yet are usually controlled by electrotonic suppression from the surrounding myocardium,[68] may serve as triggers of ventricular arrhythmias when the action potential, and thus the refractory period, are abnormally short.

Diagnosis

As more extensively reported for idiopathic VF,[69–71] polymorphic VT in SQTS is triggered by ectopic beats demonstrating an ultrashort coupling interval. Defining "short QT," however, is far from trivial.[72] The majority of patients with genetically confirmed SQTS have a QTc ≤340 ms, but longer values are possible.[73] The fact that considerable overlapping exists between the QTc of the healthy and the LQTS populations is well established,[16] and similar overlapping exists between the healthy and the SQTS populations.[72]

Treatment

As for other forms of polymorphic VT triggered by short-coupled extrasystoles, quinidine is effective therapy for SQTS-related arrhythmic storms when other drugs that prolong the QT interval (like amiodarone) fail.[74,75] Some data suggest that disopyramide may be effective.[76]

Idiopathic Ventricular Fibrillation and Early Repolarization

Terminology

The term "idiopathic" implies unknown cause and mechanism. However, patients with true idiopathic VF (as opposed to the more general category of patients with unexplained cardiac arrest), have a stereotypic phenotype described 3 decades ago[69] that includes: (1) a strictly normal ECG (with a QT interval often in the short range of normal)[77]; (2) arrhythmia onset with ultrashort coupling interval (the shortest of all polymorphic VT types [Figure 4])[78]; and (3) strikingly similar arrhythmias during repeated episodes (Figure 4A and 4B). Because of the ultrashort coupling interval, the term "short-coupled VF" was recently adopted.[79] This is interesting because, historically (3 decades ago), the phrase "short-coupled variant of torsade de pointes"[80] was used to describe an identical disease. Finally, patients with idiopathic VF who have an early repolarization ECG pattern during sinus rhythm are diagnosed as malignant early repolarization or J-wave syndrome.[57,81] Patients with J-wave syndrome are more often of the male sex, with shorter QT intervals, and appear to have a higher risk of VF recurrence than idiopathic VF patients with a normal ECG.[82,83] The arrhythmias of these subgroups are undistinguishable.[82,83]

Mechanism

Endocardial mapping during arrhythmic storms demonstrate that the ectopic beats with ultrashort coupling interval that trigger VF episodes originate from Purkinje fibers.[71,84,85] The site of origin of VF-triggering Purkinje ectopics varies by sex: right ventricular Purkinje ectopics predominate in males.[85]

It is important to note that the normal Purkinje fiber displays automaticity related to spontaneous calcium sparks released via channels unique to Purkinje cells.[68,86] Normally, this spontaneous activity within Purkinje cells is suppressed by electrotonic influences from surrounding tissues.[68] It is not entirely clear if the fundamental abnormality during Purkinje-initiated arrhythmias in idiopathic VF is an abnormal Purkinje physiology, dysfunction of the myocardium surrounding the firing Purkinje fibers, or both. Different mechanisms may take place in different patients. For example, a primary abnormality of Purkinje physiology was described in a large family with idiopathic VF caused by a gain-of-function genetic mutation in the DPP6 (dipeptidyl peptidase-like protein-6) gene.[87] In the nondiseased heart, DPP6 is responsible for a subunit of the transient outward (I_{To}) repolarizing current, which is more overtly expressed in Purkinje fibers than in myocardial cells. Consequently, when mutations in DPP6 lead to excessive I_{To} repolarizing current, shortening of the action potential is more pronounced in Purkinje fibers than in the surrounding myocardium. This allows reentry within the Purkinje–myocardium junction (short-coupled VF) in the setting of a normal QT interval.[87] On the other hand, some data suggest that patients with idiopathic VF have QT intervals shorter than those recorded in healthy controls, particularly during slow heart rate.[77,88,89] A period of voltage-dependent supernormal excitability is prominent in Purkinje fibers.[90] Short refractory periods in the surrounding myocardium would allow propagation of the EADs present in healthy Purkinje fibers during the vulnerable period of ventricular repolarization, triggering VF. Finally, among patients with idiopathic VF who have the early repolarization pattern, areas of fragmented potentials denoting abnormally slow conduction exist in the epicardial surface of the inferior wall of the right ventricle.[91]

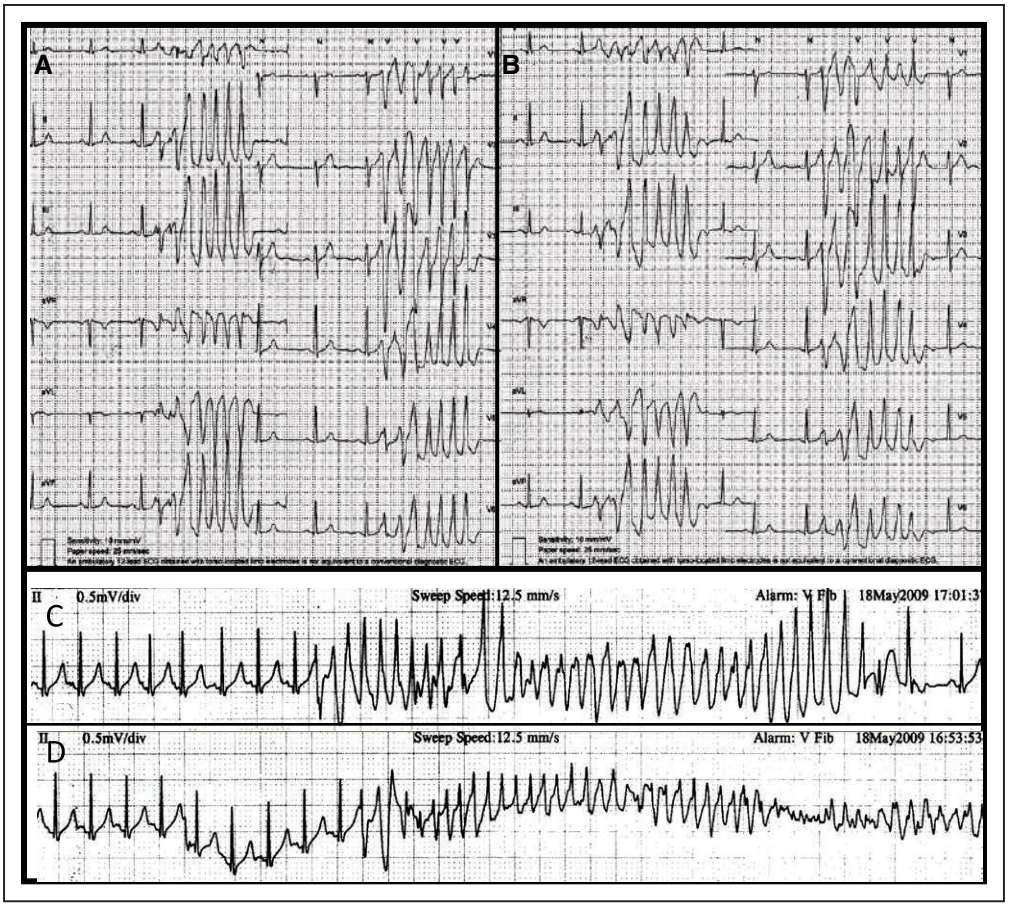

Figure 4. Polymorphic ventricular tachycardia in idiopathic ventricular fibrillation.
A and **B**, Two different episodes of spontaneous polymorphic ventricular tachycardia in a young male who survived a cardiac arrest episode at the age of 19. His QTc is 362 ms, representing the low normal range (5th percentile) of the QTc of healthy males. Note the very short coupling interval triggering the arrhythmia (coupling interval of 270 ms for both events). Not only is the first complex of the ventricular tachycardia identical for both events, but the 2nd to 5th QRS complexes of both events are very similar in the 12-lead recordings. **C** and **D**, An arrhythmic storm of a female patient with idiopathic ventricular fibrillation. These traces are recorded at paper speed of 12.5 mm/s. The coupling interval is short (351 ms). The first event terminates spontaneously after 10 s, and the second one (as well as numerous additional episodes not shown) required DC shock for termination. Both patients have been free of arrhythmias for more than a decade while on quinidine therapy.

Diagnosis

Idiopathic VF strikes at rest, often as a presenting symptom.[69,85] In its classic definition, the diagnosis of idiopathic VF is made *by exclusion* of all possible causes of VF. However, the diagnosis is made *by inclusion* once the characteristic mode of VF onset (by extrasystoles with ultrashort coupling interval) is recorded. At that point, the differential diagnosis is reduced to the few entities causing short-coupled polymorphic VT–like ischemic VF (including coronary spasm), Brugada syndrome, and SQTS. Once ischemic VF is excluded, the remaining options are highly responsive to quinidine therapy.

Emergency Therapy

The acute response of idiopathic VF to quinidine therapy was reported as early as 1929.[92] In 1949, Moe reported a young patient presenting with arrhythmic storm because of idiopathic VF.[93] This patient remained free of arrhythmias for 40 years on quinidine therapy, lived longer than the author, and was reported on again in 1990.[94] Case series[95] and reviews of all case reports published by 1990[69,70] established the efficacy of quinidine. Idiopathic VF with early repolarization also responds to quinidine.[82] Isoproterenol is also effective.[82] Verapamil was proposed as therapy for the short-coupled variant of torsade de pointes[80] (a disease that, as mentioned, is indistinguishable from idiopathic VF). Anecdotal reports show suppression of the ectopic beats triggering VF by verapamil.[96] However, verapamil was ineffective for preventing VF recurrence in patients with early repolarization.[81,82] The use of quinidine for patients with idiopathic VF or Brugada syndrome presenting with arrhythmic storm is endorsed by current guidelines[97,98] and consensus documents.[57]

Idiopathic Polymorphic VT From the RVOT

Terminology

The RVOT is the most common site of origin of benign ventricular arrhythmias in patients without organic heart disease.[70] Patients present with palpitations related to

premature ventricular complexes or salvos of nonsustained monomorphic VT. These arrhythmias are well tolerated even in cases with sustained monomorphic VT.[70]

In 2005, our group[35] and the group of Noda and Shimizu[37] described cases with otherwise typical idiopathic RVOT-VT who also developed malignant syncope or cardiac arrest caused by polymorphic VT also originating from the RVOT. It has been reported that 3% of patients with idiopathic RVOT-VT have polymorphic VT,[36] but selection bias probably leads to overestimation of this risk.

In our small series, RVOT–polymorphic VT was invariably initiated by RVOT ectopics with short coupling interval.[35] Because in roughly half of patients with idiopathic VF (reported by Haissaguerre), the arrhythmia originates in the RVOT,[71,85] one could argue that this malignant RVOT-VT simply represents idiopathic VF originating from the RVOT. However, in contrast with idiopathic VF patients, who do *not* display monomorphic VT, patients with malignant polymorphic VT have well-tolerated monomorphic VT as their prominent arrhythmia. The ectopic beats initiating monomorphic and polymorphic arrhythmias were of similar morphology, but had shorter coupling intervals during polymorphic events (350±20 ms vs. 440±80 ms).[35] Intriguingly, in the larger series by Noda,[37] only half of polymorphic RVOT-VT events displayed short coupling intervals (of ≤400 ms).

Mechanism

Idiopathic RVOT arrhythmias are attributable to triggered activity.[70] Polymorphic VT/VF that is triggered by ectopic beats with a short coupling interval could well represent the "normal" response to timed electric stimuli falling on the "vulnerable phase" (when the dispersion of ventricular refractoriness is greatest).[99] Initiation of polymorphic VT by an extrasystole falling after the end of the preceding T-wave could represent a burst of delayed afterdepolarizations in which the first one is concealed but lowers the fibrillation threshold for subsequent stimulus.[36]

Diagnosis

The typical patient is an otherwise healthy adult (39 to 45 years of age), with a 6- to 10-year history of palpitations, presenting with malignant syncope. Most patients (56% to 85% of patients in different series) are female.[36] The sinus complexes are normal. The initiating beat has an inferior axis and an LBBB pattern, denoting the RVOT origin. The polymorphic VT is fast (mean cycle length, 224 to 270 ms, as compared with 330 to 380 ms for idiopathic monomorphic VT).[36]

Emergency Therapy

Practically all reported cases of idiopathic polymorphic RVOT-VT underwent radiofrequency ablation of the RVOT extrasystoles. Consequently, there is no data on the response of this form of polymorphic VT to antiarrhythmic therapy. In cases with pause-dependent polymorphic RVOT-VT, atrial pacing at 80/min has been successfully used to prevent recurrence until the ablation is performed.[36]

Drug-Induced Polymorphic VT Without QT Prolongation

Although drug-induced polymorphic VT is almost invariably attributable to a drug-induced LQTS, a novel proarrhythmic syndrome of polymorphic VT triggered by short-coupled ventricular extrasystoles in the absence of QT prolongation has been attributed to azithromycin therapy.[38] Azithromycin potentiates depolarizing sodium current.[38] How this increased intracellular sodium loading provokes these arrhythmias remains to be explained. Similar arrhythmias have been described among patients treated with ibrutinib for blood malignancies.[100] Arrhythmia suppression with quinidine allowed for continuous ibrutinib therapy.[100]

Polymorphic VT Caused by Organic Heart Disease

This category includes: (1) patients with ischemic VF (polymorphic VT caused by acute myocardial ischemia); and (2) Purkinje-related polymorphic VT in patients with coronary disease without evident ischemia.

Ischemic VF

Terminology

The term "ischemic VF" is reserved for patients developing polymorphic VT/VF during obvious myocardial ischemia. It is recorded after positive exercise tests in patients with significant coronary artery disease, during acute coronary spasm, and more commonly, at the time of hospitalization with acute ST-segment elevation myocardial infarction (Figure 5).[101] This is a common arrhythmia. The first clinical manifestation of myocardial ischemia in patients with established, yet undiagnosed, coronary disease is often out-of-hospital sudden death attributable to ischemic VF.

Mechanism

Numerous mechanisms (reviewed by Luqman[102] and DiDiego and Antzelevitch[103]) coexist in animal models of ischemic VF. At the cellular level, acute ischemia opens ATP-sensitive potassium current channels and causes acidosis and hypoxia of myocardial cells. At the tissue level, extracellular potassium modulates cardiac automaticity and excitability, while causing a large dispersion of repolarization across the border zone, allowing phase 2 reentry. Abnormalities of intracellular calcium homeostasis also occur. Acute ischemia depresses conduction velocity, eventually causing unidirectional block and reentry.[102] A dog model of provoked ischemia (coronary artery ligation) during exercise reveals that some dogs have an inherent predisposition to ischemic VF.[104] Susceptibility to ischemic VF also exists in humans. Among patients presenting with a first myocardial infarction, those with family history of sudden death have a 3-fold increased risk of developing primary VF during the ischemic event.[105] Also, the presence of early repolarization in the preinfarction ECG, correlates with an increased risk of VF during acute ischemia.[106]

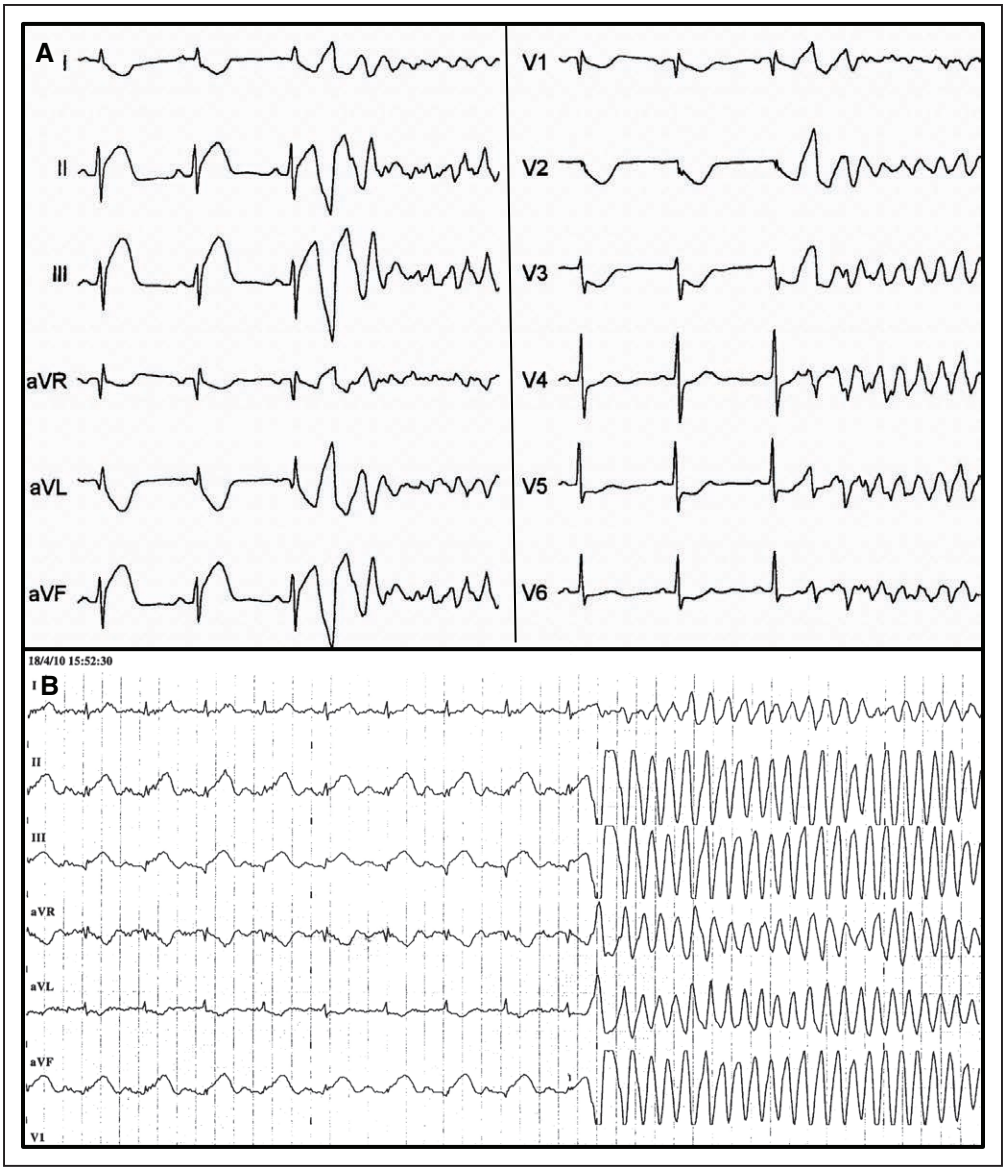

Figure 5. Ischemic ventricular fibrillation.
Two different patients with spontaneous polymorphic ventricular tachycardia deteriorating to ventricular fibrillation during acute ST-elevation inferior infarction. Note the very short coupling interval triggering the ventricular fibrillation (coupling interval of 252 ms in **B**), as short as observed in idiopathic ventricular fibrillation (see Figure 4).

Diagnosis

The ECG of ischemic VF, as described 3 decades ago,[101] demonstrates 2 important characteristics: (1) polymorphic VT starts during maximal ST-segment elevation; higher cumulative ST-segment elevation correlates with a higher risk of VF;[105] and (2) ischemic VF is triggered by short-coupled ventricular extrasystoles.[101] In a recent study comparing ischemic VF to other forms of polymorphic VT,[18] the coupling interval of the triggering beat was shortest for ischemic VF. In fact, the ultrashort coupling interval during initiation of ischemic VF (305±53 ms) is comparable only to that of idiopathic VF (320±52 ms).[78]

The differential diagnosis includes Brugada syndrome and malignant early repolarization, causing VF during ST elevation in the anterior and the inferior wall,[107] respectively.

Emergency Therapy

Guidelines endorse the use of intravenous β-blockers (use of amiodarone and lidocaine should be considered), deep sedation, and urgent revascularization during recurrent events of ischemic VF.[97] Urgent revascularization is mandatory. However, drug-refractory, incessant episodes of VF at the time of acute infarction may impede transportation to the catheterization room. Use of mechanical chest compression machines have been used during transportation and during urgent revascularization in patients with incessant VF, but survival was dismal.[108] Intravenous quinidine is readily available in for the treatment

of malaria. Considering the electrocardiographic and electrophysiological similarities to quinidine-responsive entities (like Brugada syndrome), quinidine could prove to be of value for ischemic VF.[109] Actually, in animal models of ischemic arrhythmias in rats, pigs, and dogs, quinidine was more effective than lidocaine and procainamide.[109]

Polymorphic VT in Patients With Coronary Heart Disease Without Acute Ischemia

Terminology

Polymorphic VT with unique ECG characteristics may strike in patients with coronary artery disease in the absence of acute ischemia.[110–112] Arrhythmic storms tend

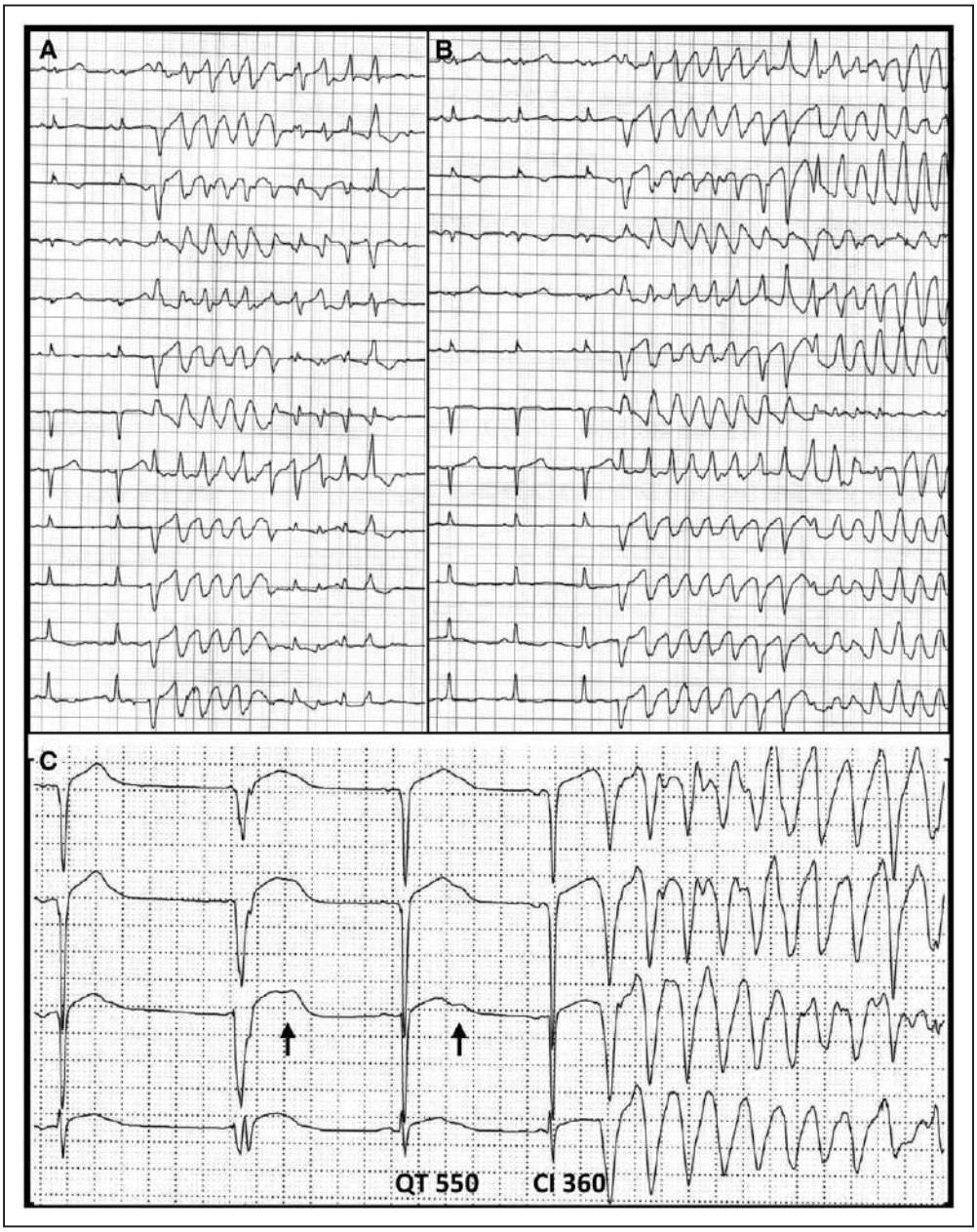

Figure 6. Purkinje-related (quinidine-responsive) polymorphic ventricular tachycardia in patients with coronary disease not related to acute myocardial ischemia.

A and **B**, Two episodes of polymorphic ventricular tachycardia (with normal QT interval and no evidence of ischemia) during an arrhythmic storm taking place 7 days after an otherwise uncomplicated coronary bypass surgery. This patient failed to respond to intravenous lidocaine, magnesium, and amiodarone but responded to quinidine therapy. (Reproduced from Viskin et al.[110]) **C**, A 51-year-old male originally presented with acute anterior infarction and was treated with percutaneous revascularization (not shown). Four days later, he developed an arrhythmic storm with frequent polymorphic ventricular tachycardia. Because of failed amiodarone therapy, the QT is not only very long (QTc, 511 ms), but also has highly abnormal morphology with notched T-waves (arrows). However, this arrhythmia is *not* torsade de pointes because the coupling interval of the ventricular tachycardia is short (360 ms). The short coupling interval demonstrates that the polymorphic ventricular tachycardia is taking place despite long QT and not because of it (representing pseudo–torsade de pointes). Despite the QT prolongation, this patient was treated with quinidine and responded. (Reproduced from Rosso et al.[18]) CI indicates coupling interval.

to occur within days of an acute myocardial infarction or coronary revascularization procedure,[110,112] but similar arrhythmias have been described in patients presenting with syncope or out-of-hospital cardiac arrest.[111,112] Because of the critical role of Purkinje fibers in triggering these arrhythmias, "His-Purkinje–related VF"[68] and "angry Purkinje syndrome"[61] have been proposed; because these arrhythmias are particularly sensitive to quinidine and refractory to all other antiarrhythmic drugs, "quinidine-responsive polymorphic VT in patients with coronary disease"[110,111] has been used.

Mechanism

The ectopic beats that trigger these VF episodes originate from Purkinje fibers located within the border zones of the infarct scar, or less commonly, deep within the infarct-related scar.[112] Purkinje fibers are less vulnerable to ischemia than myocytes and Purkinje activity remains in areas of myocardial necrosis.[113] This allows calcium spark–driven, phase-2 EADs in Purkinje fibers—normally suppressed by electric coupling from the surrounding myocardium—to propagate.[68] In these circumstances, unidirectional block and reentry within the arboreous junctions between Purkinje fibers and myocardial cells cause very fast arrhythmias.[68]

Diagnosis

The typical patient is 3 to 5 days post–acute myocardial infarction that was treated with urgent coronary stenting and had an uncomplicated hospitalization course, and then develops unforeseen VF. Continuous, multiple-lead ECG monitors do not demonstrate ST-segment changes suggestive of ischemia (Figure 6A). Instead, monitors are likely to reveal that ventricular extrasystoles of a single morphology and short coupling interval have been present (yet unnoticed) for hours. Eventually, one of these short-coupled ectopics triggers polymorphic VT.[110] The coupling interval is 358±38 ms, not as short as in ischemic VF.[18]

The Concept of Pseudo–Torsade de Pointes. About 40% of patients with Purkinje-related polymorphic VT have a very long QT interval[110] (either because the QT interval generally prolongs during the healing phase of myocardial infarction[114] or because they were on amiodarone therapy at the time of the arrhythmia [Figure 6B]). In many of these patients, the initiation of polymorphic VT is pause-dependent,[110] potentially leading to an incorrect diagnosis of torsade de pointes. We termed this condition "pseudo–torsade de pointes"[115] to emphasize the difference between a polymorphic VT *caused* by a long QT ("true torsade de pointes"), and polymorphic VT occurring *despite* QT prolongation (pseudo–torsade de pointes). The QT interval of torsade de pointes is longer (QTc, 565±76 ms vs. 491±25 ms; $P<0.001$), but considerable overlap exists between the QT of both true and pseudo–torsade de pointes.[18] On the other hand, the coupling interval in pseudo–torsade de pointes is much shorter than during torsade (360±38 ms vs. 600±173 ms). A coupling interval ≤400 ms generally indicates polymorphic VT unrelated to a LQTS even if the QT interval is prolonged.[18]

Emergency Therapy

American Heart Association guidelines state that intravenous amiodarone has a role in reducing recurrent VT/VF during resuscitation.[97] These recommendations are based on studies of out-of-hospital cardiac arrest with VF where polymorphic VT was not necessarily the initial arrhythmia. Arrhythmic storms caused by Purkinje-related VT often fail to respond to conventional antiarrhythmic drugs, including amiodarone.[110–112] Urgent catheterization is rarely helpful: it generally shows that the stent implanted at the time of hospitalization with acute infarction is patent. Even if stenotic lesions in a nonculprit artery are stented, arrhythmic storms usually continue.[110–112] Current guidelines emphasize the need for assessment of graft patency when an arrhythmic storm attributable to polymorphic VT strikes within days after coronary bypass surgery.[97] In our experience, arrhythmic storms respond to revascularization in <20% of patients developing polymorphic VT shortly after bypass surgery.[110]

On the other hand, quinidine therapy is highly effective in patients who failed to respond to other drugs.[110,111] Doses used include oral quinidine sulfate 600 mg, followed by 400 mg every 3 hours until the arrhythmic storm subsides, and then 400 mg every 8 hours. The equivalent dose for hydroquinidine are 600 mg followed by 300 mg every 8 hours and then 300 mg every 12 hours. The optimal duration of quinidine therapy remains undefined. Arrhythmic storms represent a transient phenomenon and late recurrences are rare.[110,111] Radiofrequency ablation therapy targeting the Purkinje fibers that trigger VF may be lifesaving and is best indicated for patients with frequent Purkinje-related ectopics that can be mapped between VF episodes.[112] The timing of the procedure is important, as the risk of cardiogenic shock and mortality increase if therapy is delayed.[112] Thoracic epidural anesthesia and cardiac sympathetic denervation have been used effectively in selected patients with coronary disease and drug-refractory polymorphic VT.[116,117]

STEP 3: IS THE ARRHYTHMIA EXERCISE-RELATED?

Exercise-Induced Polymorphic VT

Catecholamine-Sensitive Polymorphic VT

Terminology

Catecholamine-sensitive (also called catecholaminergic) polymorphic VT (CPVT)[118] was first described by Coumel 4 decades ago[119] in children with stress-induced syncope or cardiac arrest who have normal ECG at baseline but reproducible provocation of polymorphic and/or bidirectional VT during an exercise test.[118] Bidirectional VT is similar to that recorded during digitalis toxicity.[120]

Mechanism

CPVT is a genetic disease caused by mutations in genes that encode proteins of the sarcoplasmic reticulum calcium-release complex.[121] The most common (CPVT type 1) form is autosomal-dominant and caused by gain-of-function mutations in the RYR2 (ryanodine receptor 2) gene. Other genes associated with CPVT are CASQ2 (calsequestrin 2), TRDN (triadin), CALM1 (calmodulin 1), CALM2 (calmodulin 2), and CALM3 (calmodulin 3). These genes encode different proteins that are directly involved in regulating sarcoplasmic reticulum calcium release during excitation–contraction coupling, rendering the normal increase in calcium release in response to adrenergic stimulation hyperactive.[121] The excessive diastolic calcium leads to delayed depolarizations and triggered arrhythmias. A recent review describes in detail the molecular and tissue mechanisms of CPVT.[121]

Diagnosis

CPVT typically presents in childhood as syncope or cardiac arrest during emotional or physician stress, as drowning or a near-drowning episode,[122] and more rarely in adults, as cardiac arrest unrelated to stress. The baseline ECG is normal except for sinus bradycardia. Although the QT is normal, the abnormal QT response to sudden heart rate change[123] and prominent U-waves during exercise[124] are well described. The response to exercise or isoproterenol infusion is reproducible and virtually diagnostic (Figure 7A and 7B): as the heart rate increases, atrial arrhythmias (including atrial fibrillation) and ventricular arrhythmias increase in severity from extrasystoles to ventricular bigeminy, multifocal extrasystoles, bidirectional VT, and fast nonsustained polymorphic VT that rarely trigger VF.

CPVT may remain undiagnosed in cardiac arrest survivors when the exercise test is voided, either because of anoxic brain damage or lack of awareness and negative results in all other tests, including a normal coronary angiogram, lead to a diagnosis of unexplained cardiac arrest and implantation of an implantable cardiac defibrillator. Such cases may then recur with repeated implantable cardiac defibrillator shocks for VF that characteristically start during sinus tachycardia.

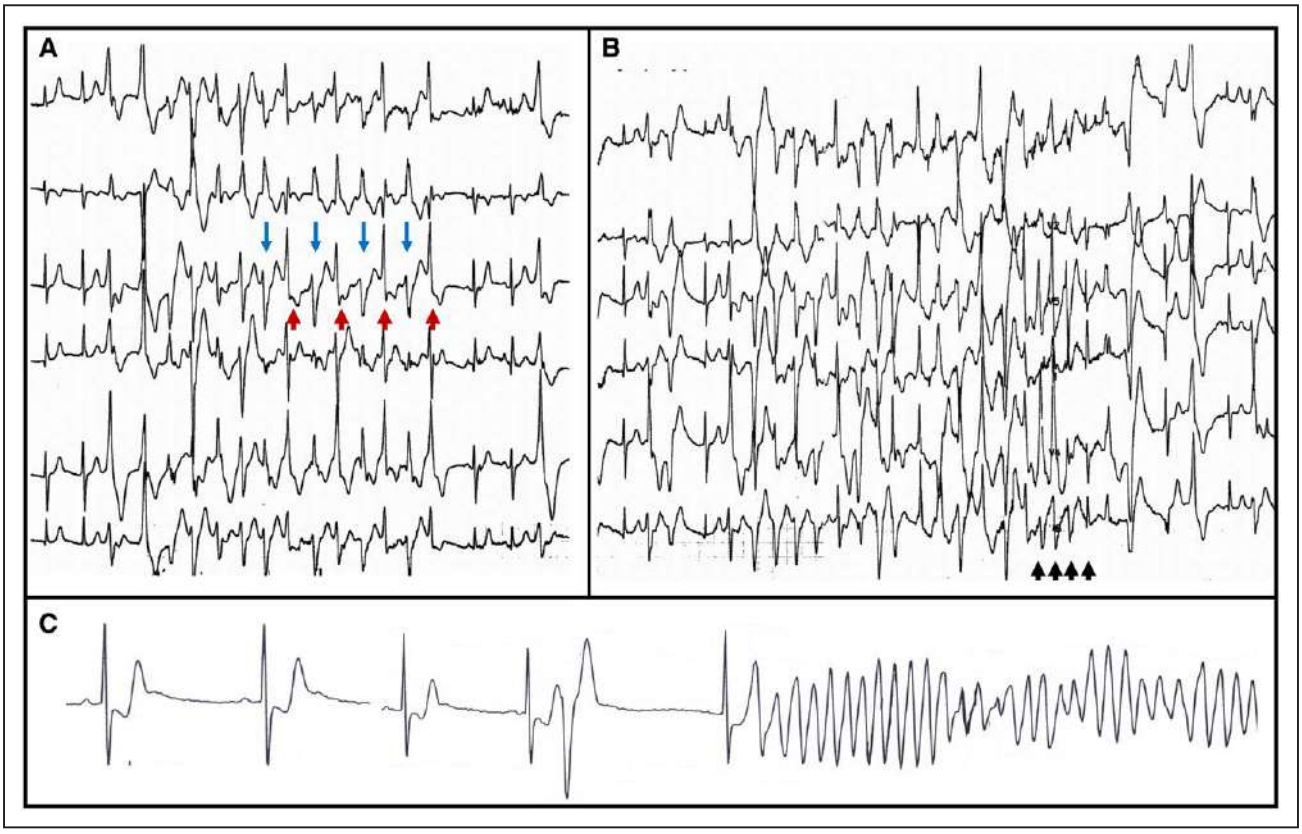

Figure 7. Exercise induced polymorphic ventricular tachycardia.
A and **B**, The exercise test of a 6-year-old boy presenting with exercise-induced syncope and diagnosed with catecholaminergic polymorphic ventricular tachycardia. The baseline ECG (not shown) is normal. **A**, At submaximal exercise, he develops bidirectional ventricular tachycardia (blue and red arrows); during maximal exercise (**B**), he develops polymorphic ventricular tachycardia that reaches a rate of 300 beats/min (black arrowheads). The child remained asymptomatic during the test, which was discontinued only because of exhaustion. He was initially treated with β-blockers; years later he was treated with β-blockers and flecainide. He has remained free of symptoms for 15 years. **C**, Recovery phase of an exercise test in a patient with coronary artery disease who developed exercise-induced ischemic ventricular fibrillation. The patient was treated with revascularization.

Therapy

Sedation to prevent immediate reinitiation of polymorphic VT is mandatory during arrhythmic storms. Long-term prevention of arrhythmias includes β-blockers at maximally-tolerated doses, but as many as 30% require additional forms of therapy because of recurrent symptoms or significant arrhythmias induced during follow-up exercise tests.[80,121,125] Class 1C drugs (flecainide or propafenone) are highly effective in CPVT by blocking RYR2 calcium channels and sodium current.[121,126] Cardiac sympathetic denervation is an effective adjuvant treatment.[127] Verapamil has been used in anecdotal cases.[128] Implantable cardiac defibrillator implantation may be life-saving but also proarrhythmic.[129] Devices should only be implanted in patients receiving full therapy with β-blockers (sympathectomy) and flecainide, and should be carefully programmed with a long detection time to delay shock delivery until triggered polymorphic VT (that is shock-refractory) deteriorates to shock-terminable VF.[130]

Exercise-Induced Ischemic VF

Patients with tight coronary lesions may develop ischemic VF during, or shortly after, an exercise test (Figure 7C). The ECG characteristics are similar those of the ischemic VF described during acute infarction (see section on Ischemic VF).

Exercise-Induced Polymorphic VT as Incidental Finding

Patients with no heart disease may develop short runs of polymorphic VT during high-intensity exercise tests, either at peak exercise or during the recovery period. In the absence of heart disease or evidence of myocardial ischemia, this arrhythmia is usually not reproducible, even if exercise tests of similar intensity are repeated several times. As an incidental finding, this arrhythmia is considered benign.

DIFFERENTIAL DIAGNOSIS AND PITFALLS

Supraventricular Arrhythmias Mimicking Polymorphic VT

Patients with Wolff-Parkinson-White syndrome may have practically normal ECGs during sinus rhythm when the atrioventricular accessory pathway connects the lateral aspect of the left atrium and ventricle. However, pathways

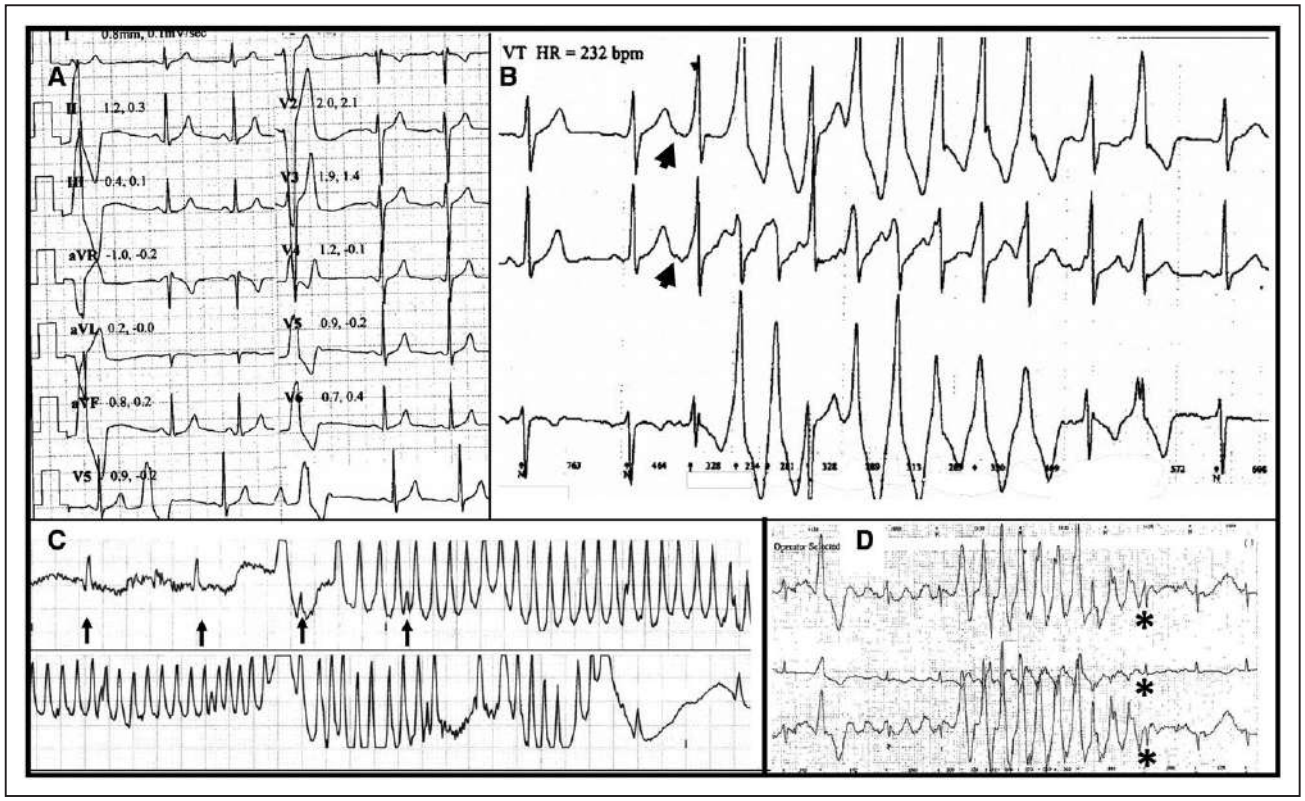

Figure 8. Mimicries of polymorphic ventricular tachycardia.
A and **B**, Baseline ECG and Holter recording of a 24-year-old male undergoing evaluation for syncope. The baseline ECG was initially interpreted as normal except for ventricular extrasystoles. However, the absence of normal Q waves in V5–V6 suggest the possibility of minor ventricular preexcitation. The tachycardia in **B** was originally interpreted as polymorphic VT (the automatic annotation printed in the ECG also mistakenly labeled the fast tachycardia as "VT"). A closer look reveals that this is atrial tachycardia (arrowhead) with ventricular preexcitation. Electrophysiological evaluation confirmed the presence of a left lateral accessory pathway that underwent ablation therapy. **C** and **D**, Examples of motion artifacts resembling polymorphic VT. **C,** The true QRS complexes (of the sinus rhythm that continues undisturbed during the artifact) can be seen "marching through" the "alleged VT," which is also too fast (faster than 350 beats/min). **D**, Termination of the alleged VT argues against the diagnosis of VT because the VT merges into the first posttachycardia sinus complex (marked with an asterisk [*]) without the pause expected after "tachycardia" termination. HR indicates heart rate; and VT, ventricular tachycardia.

with short refractory period may display 1:1 atrioventricular conduction with marked ventricular preexcitation during bursts of atrial tachycardia, leading to irregular wide complex tachycardia that may resemble nonsustained polymorphic VT—particularly if short lasting (Figure 8A and 8B).

ECG Artifacts

Motion of the ECG electrodes may create ECG traces that are difficult to distinguish from polymorphic VT. When multiple-lead recordings of the event are available, one may see the real QRS complexes of the sinus rhythm "marching through" the artifact (Figure 8C). This may be impossible during single-lead recordings. The peculiar onset of the "arrhythmia" (different from any of the modes of onset of polymorphic VT described here) or its termination (without sinus pause on cessation of "the arrhythmia") may suggest the correct diagnosis and avoid unnecessary therapy (Figure 8D).

ARTICLE INFORMATION

Affiliation

Department of Cardiology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Israel.

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Dessertenne F, Coumel P, Fabiato A. [Ventricular fibrillation and twisted peaks]. *Presse Med.* 1969;77:193–196.
2. Havakuk O, Viskin S. A tale of 2 diseases: the history of long-QT syndrome and Brugada syndrome. *J Am Coll Cardiol.* 2016;67:100–108. doi: 10.1016/j.jacc.2015.10.020
3. Viskin S. Long QT syndromes and torsade de pointes. *Lancet.* 1999;354:1625–1633. doi: 10.1016/S0140-6736(99)02107-8
4. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation.* 1998;98:2314–2322. doi: 10.1161/01.cir.98.21.2314
5. Shimizu W, Antzelevitch C. Cellular basis for long QT, transmural dispersion of repolarization, and torsade de pointes in the long QT syndrome. *J Electrocardiol.* 1999;32 (Suppl):177–184. doi: 10.1016/s0022-0736(99)90077-8
6. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004;350:1013–1022. doi: 10.1056/NEJMra032426
7. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M, Belhassen B, Hochenberg M, Viskin S. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J Am Coll Cardiol.* 2007;49:320–328. doi: 10.1016/j.jacc.2006.08.058
8. Chorin E, Hochstadt A, Viskin S, Rozovski U, Havakuk O, Baranchuk A, Enriquez A, Strasberg B, Guevara-Valdivia ME, Márquez MF, et al. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. *Heart Rhythm.* 2017;14:90–95. doi: 10.1016/j.hrthm.2016.09.013
9. Viskin S. Post-tachycardia QT prolongation: maladjustment of the QT interval to the normal heart rate. *Pacing Clin Electrophysiol.* 2003;26:659–661. doi: 10.1046/j.1460-9592.2003.00114.x
10. Halkin A, Roth A, Lurie I, Fish R, Belhassen B, Viskin S. Pause-dependent torsade de pointes following acute myocardial infarction: a variant of the acquired long QT syndrome. *J Am Coll Cardiol.* 2001;38:1168–1174. doi: 10.1016/s0735-1097(01)01468-1
11. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. *Circulation.* 1996;93:407–411. doi: 10.1161/01.cir.93.3.407
12. Chorin E, Hochstadt A, Granot Y, Khoury S, Schwartz AL, Margolis G, Barashi R, Viskin D, Ghantous E, Schnapper M, et al. Grapefruit juice prolongs the QT interval of healthy volunteers and patients with long QT syndrome. *Heart Rhythm.* 2019;16:1141–1148. doi: 10.1016/j.hrthm.2019.04.039
13. Havakuk O, Schwartz AL, Rosso R, Viskin S. A question on proarrhythmic food: Is grapefruit "the forbidden fruit" for patients with long QT syndrome? *Trends Cardiovasc Med.* 2020;30:313–314.
14. Woosley RL. Arrhythmogenic foods - a growing medical problem. *Trends Cardiovasc Med.* 2020;30:310–312. doi: 10.1016/j.tcm.2019.08.007
15. Salem JE, Waintraub X, Courtillot C, Shaffer CM, Gandjbakhch E, Maupain C, Moslehi JJ, Badilini F, Haroche J, Gougis P, et al. Hypogonadism as a reversible cause of torsades de pointes in men. *Circulation.* 2018;138:110–113. doi: 10.1161/CIRCULATIONAHA.118.034282
16. Vink AS, Neumann B, Lieve KVV, Sinner MF, Hofman N, El Kadi S, Schoenmaker MHA, Slaghekke HMJ, de Jong JSSG, Clur SB, et al. Determination and interpretation of the QT interval. *Circulation.* 2018;138:2345–2358. doi: 10.1161/CIRCULATIONAHA.118.033943
17. Tan HL, Bardai A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, Wilde AA. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation.* 2006;114:2096–2103. doi: 10.1161/CIRCULATIONAHA.106.642694
18. Rosso R, Hochstadt A, Viskin D, Chorin E, Schwartz AL, Tovia-Brodie O, Laish-Farkash A, Havakuk O, Gepstein L, Banai S, et al. Polymorphic ventricular tachycardia, ischaemic ventricular fibrillation, and torsade de pointes: importance of the QT and the coupling interval in the differential diagnosis. *Eur Heart J.* 2021.
19. Viskin S, Postema PG, Bhuiyan ZA, Rosso R, Kalman JM, Vohra JK, Guevara-Valdivia ME, Marquez MF, Kogan E, Belhassen B, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. *J Am Coll Cardiol.* 2010;55:1955–1961. doi: 10.1016/j.jacc.2009.12.015
20. Viskin S, Rosso R, Rogowski O, Belhassen B, Levitas A, Wagshal A, Katz A, Fourey D, Zeltser D, Oliva A, et al. Provocation of sudden heart rate oscillation with adenosine exposes abnormal QT responses in patients with long QT syndrome: a bedside test for diagnosing long QT syndrome. *Eur Heart J.* 2006;27:469–475. doi: 10.1093/eurheartj/ehi460
21. Viskin S, Alla SR, Barron HV, Heller K, Saxon L, Kitzis I, Hare GF, Wong MJ, Lesh MD, Scheinman MM. Mode of onset of torsade de pointes in congenital long QT syndrome. *J Am Coll Cardiol.* 1996;28:1262–1268. doi: 10.1016/s0735-1097(96)00311-7
22. Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol.* 1983;2:806–817. doi: 10.1016/s0735-1097(83)80226-5
23. Viskin S, Fish R, Zeltser D, Belhassen B, Heller K, Brosh D, Laniado S, Barron HV. Arrhythmias in the congenital long QT syndrome: how often is torsade de pointes pause dependent? *Heart.* 2000;83:661–666. doi: 10.1136/heart.83.6.661
24. Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T-U waves precede torsades de pointes in long QT syndrome: a systematic electrocardiographic analysis in patients with acquired and congenital QT prolongation. *J Am Coll Cardiol.* 2009;54:143–149. doi: 10.1016/j.jacc.2009.03.043
25. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S. Treatment of torsade de pointes with magnesium sulfate. *Circulation.* 1988;77:392–397. doi: 10.1161/01.cir.77.2.392
26. Cosio FG, Goicolea A, López Gil M, Kallmeyer C, Barroso JL. Suppression of torsades de pointes with verapamil in patients with atrioventricular block. *Eur Heart J.* 1991;12:635–638. doi: 10.1093/oxfordjournals.eurheartj.a059952
27. Shimizu W, Ohe T, Kurita T, Kawade M, Arakaki Y, Aihara N, Kamakura S, Kamiya T, Shimomura K. Effects of verapamil and propranolol on early afterdepolarizations and ventricular arrhythmias induced by epinephrine in congenital long QT syndrome. *J Am Coll Cardiol.* 1995;26:1299–1309. doi: 10.1016/0735-1097(95)00313-4
28. Yang T, Chun YW, Stroud DM, Mosley JD, Knollmann BC, Hong C, Roden DM. Screening for acute IKr block is insufficient to detect torsades de pointes liability: role of late sodium current. *Circulation.* 2014;130:224–234. doi: 10.1161/CIRCULATIONAHA.113.007765

29. Lei M, Wu L, Terrar DA, Huang CL. Modernized classification of cardiac antiarrhythmic drugs. *Circulation.* 2018;138:1879–1896. doi: 10.1161/CIRCULATIONAHA.118.035455
30. Bos JM, Crotti L, Rohatgi RK, Castelletti S, Dagradi F, Schwartz PJ, Ackerman MJ. Mexiletine shortens the QT interval in patients with potassium channel-mediated type 2 long QT syndrome. *Circ Arrhythm Electrophysiol.* 2019;12:e007280. doi: 10.1161/CIRCEP.118.007280
31. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, Novelli V, Baiardi P, Bagnardi V, Etheridge SP, et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J Am Coll Cardiol.* 2016;67:1053–1058. doi: 10.1016/j.jacc.2015.12.033
32. Badri M, Patel A, Patel C, Liu G, Goldstein M, Robinson VM, Xue X, Yang L, Kowey PR, Yan GX. Mexiletine prevents recurrent torsades de pointes in acquired long QT syndrome refractory to conventional measures. *JACC Clin Electrophysiol.* 2015;1:315–322. doi: 10.1016/j.jacep.2015.05.008
33. Dumaine R, Kirsch GE. Mechanism of lidocaine block of late current in long Q-T mutant Na+ channels. *Am J Physiol.* 1998;274:H477–H487. doi: 10.1152/ajpheart.1998.274.2.H477
34. Viskin S, Rosso R. J-wave syndromes. In: Zipes DP, Jalife J, Stevenson GW, eds. *Cardiac Electrophysiology: From Cell to Beside.* 7th ed. Elsevier; 2018:917–925.
35. Viskin S, Rosso R, Rogowski O, Belhassen B. The "short-coupled" variant of right ventricular outflow ventricular tachycardia: a not-so-benign form of benign ventricular tachycardia? *J Cardiovasc Electrophysiol.* 2005;16:912–916. doi: 10.1111/j.1540-8167.2005.50040.x
36. Viskin S. Idiopathic polymorphic ventricular tachycardia: a "benign disease" with a touch of bad luck? *Korean Circ J.* 2017;47:299–306. doi: 10.4070/kcj.2016.0303
37. Noda T, Shimizu W, Taguchi A, Aiba T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. *J Am Coll Cardiol.* 2005;46:1288–1294. doi: 10.1016/j.jacc.2005.05.077
38. Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, Luis PB, Hall L, Zhang W, Du L, et al. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol.* 2017;10:e003560. doi: 10.1161/CIRCEP.115.003560
39. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol.* 1992;20:1391–1396. doi: 10.1016/0735-1097(92)90253-j
40. Chiale PA, Garro HA, Fernández PA, Elizari MV. High-degree right bundle branch block obscuring the diagnosis of Brugada electrocardiographic pattern. *Heart Rhythm.* 2012;9:974–976. doi: 10.1016/j.hrthm.2012.01.028
41. Richter S, Sarkozy A, Veltmann C, Chierchia GB, Boussy T, Wolpert C, Schimpf R, Brugada J, Brugada R, Borggrefe M, et al. Variability of the diagnostic ECG pattern in an ICD patient population with Brugada syndrome. *J Cardiovasc Electrophysiol.* 2009;20:69–75. doi: 10.1111/j.1540-8167.2008.01282.x
42. Viskin S. Radiofrequency ablation of asymptomatic Brugada syndrome: don't go burning my heart. *Circulation.* 2018;137:1883–1884. doi: 10.1161/CIRCULATIONAHA.117.032624
43. Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, Jamal SM, Szybowska M, Morel CF, Bowdin S, et al; National Institutes of Health Clinical Genome Resource Consortium. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation.* 2018;138:1195–1205. doi: 10.1161/CIRCULATIONAHA.118.035070
44. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat Genet.* 2013;45:1044–1049. doi: 10.1038/ng.2712
45. Tadros R, Tan HL, El Mathari S, Kors JA, Postema PG, Lahrouchi N, Beekman L, Radivojkov-Blagojevic M, Amin AS, Meitinger T, et al; ESCAPE-NET Investigators. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. *Eur Heart J.* 2019;40:3097–3107. doi: 10.1093/eurheartj/ehz435
46. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. *J Mol Cell Cardiol.* 2010;49:543–553. doi: 10.1016/j.yjmcc.2010.07.012
47. Zhang J, Sacher F, Hoffmayer K, O'Hara T, Strom M, Cuculich P, Silva J, Cooper D, Faddis M, Hocini M, et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients. *Circulation.* 2015;131:1950–1959. doi: 10.1161/CIRCULATIONAHA.114.013698
48. Milman A, Andorin A, Gourraud JB, Postema PG, Sacher F, Mabo P, Kim SH, Juang JJM, Maeda S, Takahashi Y, et al. Profile of patients with Brugada syndrome presenting with their first documented arrhythmic event: data from the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS). *Heart Rhythm.* 2018;15:716–724. doi: 10.1016/j.hrthm.2018.01.014
49. Eggebrecht H, Wieneke H, Erbel R. Image of the month. Brugada-like ECG pattern in a patient with isolated right ventricular infarction. *Herz.* 2009;34:327. doi: 10.1007/s00059-009-3241-6
50. Shan P, Lin J, Xu W, Huang W. ST-segment elevation after direct current shock mimicking acute myocardial infarction: a case report and review of the literature. *Am J Emerg Med.* 2014;32:1438.e1–1438.e3. doi: 10.1016/j.ajem.2014.04.005
51. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol.* 1996;27:1061–1070. doi: 10.1016/0735-1097(95)00613-3
52. Shimeno K, Takagi M, Maeda K, Tatsumi H, Doi A, Yoshiyama M. Usefulness of multichannel Holter ECG recording in the third intercostal space for detecting type 1 Brugada ECG: comparison with repeated 12-lead ECGs. *J Cardiovasc Electrophysiol.* 2009;20:1026–1031. doi: 10.1111/j.1540-8167.2009.01490.x
53. Tadros R, Nannenberg EA, Lieve KV, Škorić-Milosavljević D, Lahrouchi N, Lekanne Deprez RH, Vendrik J, Reckman YJ, Postema PG, Amin AS, et al. Yield and pitfalls of ajmaline testing in the evaluation of unexplained cardiac arrest and sudden unexplained death: single-center experience with 482 families. *JACC Clin Electrophysiol.* 2017;3:1400–1408. doi: 10.1016/j.jacep.2017.04.005
54. Viskin S, Rosso R. Read my lips: a positive ajmaline test does not always mean you have Brugada syndrome. *JACC Clin Electrophysiol.* 2017;3:1409–1411. doi: 10.1016/j.jacep.2017.05.016
55. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AA. Everybody has Brugada syndrome until proven otherwise? *Heart Rhythm.* 2015;12:1595–1598. doi: 10.1016/j.hrthm.2015.04.017
56. Poli S, Toniolo M, Maiani M, Zanuttini D, Rebellato L, Vendramin I, Dametto E, Bernardi G, Bassi F, Napolitano C, et al. Management of untreatable ventricular arrhythmias during pharmacologic challenges with sodium channel blockers for suspected Brugada syndrome. *Europace.* 2018;20:234–242. doi: 10.1093/europace/eux092
57. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Heart Rhythm.* 2016;13:e295–e324. doi: 10.1016/j.hrthm.2016.05.024
58. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation.* 2004;110:1731–1737. doi: 10.1161/01.CIR.0000143159.30585.90
59. Viskin S, Wilde AAM, Guevara-Valdivia ME, Daoulah A, Krahn A, Zipes DP, Halkin A, Shivkumar K, Boyle NG, Adler A, et al. Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries. *J Am Coll Cardiol.* 2013. doi: 10.1016/j.jacc.2013.02.077
60. Viskin S, Antzelevitch C, Márquez MF, Belhassen B. Quinidine: a valuable medication joins the list of 'endangered species'. *Europace.* 2007;9:1105–1106. doi: 10.1093/europace/eum181
61. Viskin S, Schwartz AL, Levi Y, Hochstadt A, Rosso R. Ventricular fibrillation after ablation of a benign arrhythmia. Angry Purkinje syndrome? *HeartRhythm Case Rep.* 2020;6:937–941. doi: 10.1016/j.hrcr.2020.09.010
62. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation.* 2011;123:1270–1279. doi: 10.1161/CIRCULATIONAHA.110.972612
63. Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, Bjerregaard P. Idiopathic short QT interval: a new clinical syndrome? *Cardiology.* 2000;94:99–102. doi: 10.1159/000047299
64. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation.* 2003;108:965–970. doi: 10.1161/01.CIR.0000085071.28695.C4

65. Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. *Circ Arrhythm Electrophysiol.* 2010;3:401–408. doi: 10.1161/CIRCEP.109.921056
66. Patel C, Antzelevitch C. Cellular basis for arrhythmogenesis in an experimental model of the SQT1 form of the short QT syndrome. *Heart Rhythm.* 2008;5:585–590. doi: 10.1016/j.hrthm.2008.01.022
67. Shinnawi R, Shaheen N, Huber I, Shiti A, Arbel G, Gepstein A, Ballan N, Setter N, Tijsen AJ, Borggrefe M, et al. Modeling reentry in the short QT syndrome with human-induced pluripotent stem cell-derived cardiac cell sheets. *J Am Coll Cardiol.* 2019;73:2310–2324. doi: 10.1016/j.jacc.2019.02.055
68. Haissaguerre M, Vigmond E, Stuyvers B, Hocini M, Bernus O. Ventricular arrhythmias and the His-Purkinje system. *Nat Rev Cardiol.* 2016;13:155–166. doi: 10.1038/nrcardio.2015.193
69. Viskin S, Belhassen B. Idiopathic ventricular fibrillation. *Am Heart J.* 1990;120:661–671. doi: 10.1016/0002-8703(90)90025-s
70. Belhassen B, Viskin S. Idiopathic ventricular tachycardia and fibrillation. *J Cardiovasc Electrophysiol.* 1993;4:356–368. doi: 10.1111/j.1540-8167.1993.tb01236.x
71. Haïssaguerre M, Shoda M, Jaïs P, Nogami A, Shah DC, Kautzner J, Arentz T, Kalushe D, Lamaison D, Griffith M, et al. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation.* 2002;106:962–967. doi: 10.1161/01.cir.0000027564.55739.b1
72. Viskin S. The QT interval: too long, too short or just right. *Heart Rhythm.* 2009;6:711–715. doi: 10.1016/j.hrthm.2009.02.044
73. Bjerregaard P, Gussak I. Short QT syndrome: mechanisms, diagnosis and treatment. *Nat Clin Pract Cardiovasc Med.* 2005;2:84–87. doi: 10.1038/ncpcardio0097
74. Mazzanti A, Maragna R, Vacanti G, Kostopoulou A, Marino M, Monteforte N, Bloise R, Underwood K, Tibollo V, Pagan E, et al. Hydroquinidine prevents life-threatening arrhythmic events in patients with short QT syndrome. *J Am Coll Cardiol.* 2017;70:3010–3015. doi: 10.1016/j.jacc.2017.10.025
75. Spartalis M, Livanis E, Spartalis E, Tsoutsinos A. Electrical storm in an acquired short QT syndrome successfully treated with quinidine. *Clin Case Rep.* 2019;7:1617–1618. doi: 10.1002/ccr3.2282
76. McPate MJ, Duncan RS, Witchel HJ, Hancox JC. Disopyramide is an effective inhibitor of mutant HERG K+ channels involved in variant 1 short QT syndrome. *J Mol Cell Cardiol.* 2006;41:563–566. doi: 10.1016/j.yjmcc.2006.05.021
77. Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D, Tekes-Manova D, Belhassen B. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. *Heart Rhythm.* 2004;1:587–591. doi: 10.1016/j.hrthm.2004.07.010
78. Viskin S, Lesh MD, Eldar M, Fish R, Setbon I, Laniado S, Belhassen B. Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. *J Cardiovasc Electrophysiol.* 1997;8:1115–1120. doi: 10.1111/j.1540-8167.1997.tb00997.x
79. Steinberg C, Davies B, Mellor G, Tadros R, Laksman Z, Roberts J, Green M, Alqarawi W, Krahn AD. Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report From the CASPER Registry. *Eur Heart J.* 2021. doi: 10.1093/eurheartj/ehab275
80. Leenhardt A, Glaser E, Burguera M, Nürnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. *Circulation.* 1994;89:206–215. doi: 10.1161/01.cir.89.1.206
81. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med.* 2008;358:2016–2023. doi: 10.1056/NEJMoa071968
82. Haïssaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol.* 2009;53:612–619. doi: 10.1016/j.jacc.2008.10.044
83. Viskin S. Idiopathic ventricular fibrillation "Le Syndrome d'Haïssaguerre" and the fear of J waves. *J Am Coll Cardiol.* 2009;53:620–622. doi: 10.1016/j.jacc.2008.11.011
84. Haïssaguerre M, Duchateau J, Dubois R, Hocini M, Cheniti G, Sacher F, Lavergne T, Probst V, Surget E, Vigmond E, et al. Idiopathic ventricular fibrillation: role of Purkinje system and microstructural myocardial abnormalities. *JACC Clin Electrophysiol.* 2020;6:591–608. doi: 10.1016/j.jacep.2020.03.010
85. Surget E, Cheniti G, Ramirez FD, Leenhardt A, Nogami A, Gandjbakhch E, Extramiana F, Hidden-Lucet F, Pillois X, Benoist D, et al. Sex differences in the origin of Purkinje ectopy initiating idiopathic ventricular fibrillation. *Heart Rhythm.* 2021. doi: 10.1016/j.hrthm.2021.07.007
86. Stuyvers BD, Dun W, Matkovich S, Sorrentino V, Boyden PA, ter Keurs HE. Ca2+ sparks and waves in canine Purkinje cells: a triple layered system of Ca2+ activation. *Circ Res.* 2005;97:35–43. doi: 10.1161/01.RES.0000173375.26489.fe
87. Xiao L, Koopmann TT, Ördög B, Postema PG, Verkerk AO, Iyer V, Sampson KJ, Boink GJ, Mamarbachi MA, Varro A, et al. Unique cardiac Purkinje fiber transient outward current β-subunit composition: a potential molecular link to idiopathic ventricular fibrillation. *Circ Res.* 2013;112:1310–1322. doi: 10.1161/CIRCRESAHA.112.300227
88. Fujiki A, Sugao M, Nishida K, Sakabe M, Tsuneda T, Mizumaki K, Inoue H. Repolarization abnormality in idiopathic ventricular fibrillation: assessment using 24-hour QT-RR and QaT-RR relationships. *J Cardiovasc Electrophysiol.* 2004;15:59–63. doi: 10.1046/j.1540-8167.2004.03396.x
89. Sugao M, Fujiki A, Sakabe M, Nishida K, Tsuneda T, Iwamoto J, Mizumaki K, Inoue H. New quantitative methods for evaluation of dynamic changes in QT interval on 24 hour Holter ECG recordings: QT interval in idiopathic ventricular fibrillation and long QT syndrome. *Heart.* 2006;92:201–207. doi: 10.1136/hrt.2004.059071
90. Spear JF, Moore EN. The effect of changes in rate and rhythm on supernormal excitability in the isolated Purkinje system of the dog. A possible role in re-entrant arrhythmias. *Circulation.* 1974;50:1144–1149. doi: 10.1161/01.cir.50.6.1144
91. Nademanee K, Haissaguerre M, Hocini M, Nogami A, Cheniti G, Duchateau J, Behr ER, Saba M, Bokan R, Lou Q, et al. Mapping and ablation of ventricular fibrillation associated with early repolarization syndrome. *Circulation.* 2019;140:1477–1490. doi: 10.1161/CIRCULATIONAHA.118.039022
92. Dock W. Transitory ventricular fibrillation as a cause of syncope and its prevention by quinidine sulfate. *Am Heart J.* 1929;4:709–714.
93. Moe T. Morgagni-Adams-Stokes attacks caused by transient recurrent ventricular fibrillation in a patient without apparent organic heart disease; a case report. *Am Heart J.* 1949;37:811–819. doi: 10.1016/0002-8703(49)90179-9
94. Kontny F, Dale J. Self-terminating idiopathic ventricular fibrillation presenting as syncope: a 40-year follow-up report. *J Intern Med.* 1990;227:211–213. doi: 10.1111/j.1365-2796.1990.tb00145.x
95. Belhassen B, Shapira I, Shoshani D, Paredes A, Miller H, Laniado S. Idiopathic ventricular fibrillation: inducibility and beneficial effects of class I antiarrhythmic agents. *Circulation.* 1987;75:809–816. doi: 10.1161/01.cir.75.4.809
96. Shiga T, Shoda M, Matsuda N, Fuda Y, Hagiwara N, Ohnishi S, Watanabe A, Kasanuki H. Electrophysiological characteristic of a patient exhibiting the short-coupled variant of torsade de pointes. *J Electrocardiol.* 2001;34:271–275. doi: 10.1054/jelc.2001.24380
97. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2018;138:e210–e271. doi: 10.1161/CIR.0000000000000548
98. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;36:2793–2867. doi: 10.1093/eurheartj/ehv316
99. Han J, Garcia de Jalon PD, Moe GK. Fibrillation threshold of premature ventricular responses. *Circ Res.* 1966;18:18–25. doi: 10.1161/01.res.18.1.18
100. Lampson BL, Yu L, Glynn RJ, Barrientos JC, Jacobsen ED, Banerji V, Jones JA, Walewska R, Savage KJ, Michaud GF, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood.* 2017;129:2581–2584. doi: 10.1182/blood-2016-10-742437
101. Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M. Polymorphous ventricular tachycardia associated with acute myocardial infarction. *Circulation.* 1991;84:1543–1551. doi: 10.1161/01.cir.84.4.1543

102. Luqman N, Sung RJ, Wang CL, Kuo CT. Myocardial ischemia and ventricular fibrillation: pathophysiology and clinical implications. *Int J Cardiol.* 2007;119:283–290. doi: 10.1016/j.ijcard.2006.09.016
103. Di Diego JM, Antzelevitch C. Ischemic ventricular arrhythmias: experimental models and their clinical relevance. *Heart Rhythm.* 2011;8:1963–1968. doi: 10.1016/j.hrthm.2011.06.036
104. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation.* 1988;78:969–979. doi: 10.1161/01.cir.78.4.969
105. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, Arnold AE, de Boer MJ, Gorgels AP, Michels HR, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation.* 2006;114:1140–1145.doi:10.1161/CIRCULATIONAHA.105.606145
106. Tikkanen JT, Wichmann V, Junttila MJ, Rainio M, Hookana E, Lappi OP, Kortelainen ML, Anttonen O, Huikuri HV. Association of early repolarization and sudden cardiac death during an acute coronary event. *Circ Arrhythm Electrophysiol.* 2012;5:714–718. doi: 10.1161/CIRCEP.112.970863
107. Chinushi M, Izumi D, Furushima H, Watanabe H, Aizawa Y. Multiple premature beats triggered ventricular arrhythmias during pilsicainide infusion in a patient with inferior ST-segment elevation. *Pacing Clin Electrophysiol.* 2006;29:1445–1448. doi: 10.1111/j.1540-8159.2006.00562.x
108. Kalra A, Maharaj V, Johannsen RA, Hollenberg SM. Catheterization laboratory activation during mechanical cardiopulmonary resuscitation: when should we say "No?." *Catheter Cardiovasc Interv.* 2014;83:58–64. doi: 10.1002/ccd.25167
109. Chorin E, Rosso R, Viskin D, Ben-Shoshan J, Viskin S. Arrhythmic storm from ischemic ventricular fibrillation treated with intravenous quinidine. *J Electrocardiol.* 2021. In press.
110. Viskin S, Chorin E, Viskin D, Hochstadt A, Halkin A, Tovia-Brodie O, Lee JK, Asher E, Laish-Farkash A, Amit G, et al. Quinidine-responsive polymorphic ventricular tachycardia in patients with coronary heart disease. *Circulation.* 2019;139:2304–2314. doi: 10.1161/CIRCULATIONAHA.118.038036
111. Viskin S, Hochstadt A, Chorin E, Viskin D, Havakuk O, Khoury S, Lee JK, Belhassen B, Rosso R. Quinidine-responsive out-of-hospital polymorphic ventricular tachycardia in patients with coronary heart disease. *Europace.* 2020;22:265–273. doi: 10.1093/europace/euz290
112. Komatsu Y, Hocini M, Nogami A, Maury P, Peichl P, Iwasaki YK, Masuda K, Denis A, Voglimacci-Stephanopoli Q, Wichterle D, et al. Catheter ablation of refractory ventricular fibrillation storm after myocardial infarction. *Circulation.* 2019;139:2315–2325. doi: 10.1161/CIRCULATIONAHA.118.037997
113. Friedman PL, Stewart JR, Fenoglio JJ Jr, Wit AL. Survival of subendocardial Purkinje fibers after extensive myocardial infarction in dogs. *Circ Res.* 1973;33:597–611. doi: 10.1161/01.res.33.5.597
114. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation.* 1978;57:1074–1077. doi: 10.1161/01.cir.57.6.1074
115. Viskin S, Marai I, Rosso R. Long QT syndrome and torsade de dointes ultimately treated with quinidine: introducing the concept of pseudo-torsade de pointes. *Circulation.* 2021;144:85–89. doi: 10.1161/CIRCULATIONAHA.121.054991
116. Cardona-Guarache R, Padala SK, Velazco-Davila L, Cassano A, Abbate A, Ellenbogen KA, Koneru JN. Stellate ganglion blockade and bilateral cardiac sympathetic denervation in patients with life-threatening ventricular arrhythmias. *J Cardiovasc Electrophysiol.* 2017;28:903–908. doi: 10.1111/jce.13249
117. Bourke T, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, Boyle NG, Mahajan A, Narasimhan C, Lokhandwala Y, et al. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. *Circulation.* 2010;121:2255–2262. doi: 10.1161/CIRCULATIONAHA.109.929703
118. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation.* 1995;91:1512–1519. doi: 10.1161/01.cir.91.5.1512
119. Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholaminergic-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. *Br Heart J.* 1978;40(Suppl):28–37.
120. Zimdahl WT, Townsend CE. Bidirectional ventricular tachycardia due to digitalis poisoning; response to potassium therapy and evaluation of arrhythmia mechanism. *Am Heart J.* 1954;47:304–312. doi: 10.1016/0002-8703(54)90258-6
121. Wleklinski MJ, Kannankeril PJ, Knollmann BC. Molecular and tissue mechanisms of catecholaminergic polymorphic ventricular tachycardia. *J Physiol.* 2020;598:2817–2834. doi: 10.1113/JP276757
122. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation.* 2004;110:2119–2124. doi: 10.1161/01.CIR.0000144471.98080.CA
123. Nof E, Belhassen B, Arad M, Bhuiyan ZA, Antzelevitch C, Rosso R, Fogelman R, Luria D, El-Ani D, Mannens MM, et al. Postpacing abnormal repolarization in catecholaminergic polymorphic ventricular tachycardia associated with a mutation in the cardiac ryanodine receptor gene. *Heart Rhythm.* 2011;8:1546–1552. doi: 10.1016/j.hrthm.2011.05.016
124. Aizawa Y, Komura S, Okada S, Chinushi M, Aizawa Y, Morita H, Ohe T. Distinct U wave changes in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). *Int Heart J.* 2006;47:381–389. doi: 10.1536/ihj.47.381
125. Leenhardt A, Denjoy I, Guicheney P. Catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2012;5:1044–1052. doi: 10.1161/CIRCEP.111.962027
126. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med.* 2009;15:380–383. doi: 10.1038/nm.1942
127. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, Ferrandi C, Koolbergen DR, Odero A, Schwartz PJ. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med.* 2008;358:2024–2029. doi: 10.1056/NEJMoa0708006
128. Rosso R, Kalman JM, Rogowski O, Diamant S, Birger A, Biner S, Belhassen B, Viskin S. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2007;4:1149–1154. doi: 10.1016/j.hrthm.2007.05.017
129. van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, Aiba T, Wada Y, Ingles J, Leren IS, et al. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J.* 2019;40:2953–2961. doi: 10.1093/eurheartj/ehz309
130. Miyake CY, Webster G, Czosek RJ, Kantoch MJ, Dubin AM, Avasarala K, Atallah J. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. *Circ Arrhythm Electrophysiol.* 2013;6:579–587. doi: 10.1161/CIRCEP.113.000170