

STATE-OF-THE-ART PAPER

## Ventricular Arrhythmias in the Absence of Structural Heart Disease

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Ventricular arrhythmia (VA) in structurally normal hearts can be broadly considered under non-life-threatening monomorphic and life-threatening polymorphic rhythms. Monomorphic VA is classified on the basis of site of origin in the heart, and the most common areas are the ventricular outflow tracts and left ventricular fascicles. The morphology of the QRS complexes on electrocardiogram is an excellent tool to identify the site of origin of the rhythm. Although these arrhythmias are common and generally carry an excellent prognosis, rare sudden death events have been reported. Very frequent ventricular ectopy may also result in a cardiomyopathy in a minority of patients. Suppression of VA may be achieved using calcium-channel blockers, beta-adrenergic blockers, and class I or III antiarrhythmic drugs. Radiofrequency ablation has emerged as an excellent option to eliminate these arrhythmias, although certain foci including aortic cusps and epicardium may be technically challenging. Polymorphic ventricular tachycardia (VT) is rare and generally occurs in patients with genetic ion channel disorders including long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, and short QT syndrome. Unlike monomorphic VT, these arrhythmic syndromes are associated with sudden death. While the cardiac gross morphology is normal, suggesting a structurally normal heart, abnormalities exist at the molecular level and predispose them to arrhythmias. Another fascinating area, idiopathic ventricular fibrillation and early repolarization syndrome, are undergoing research for a genetic basis. (J Am Coll Cardiol 2012;59:1733-44) © 2012 by the American College of Cardiology Foundation

Patients with ventricular arrhythmia (VA) require an evaluation to determine if structural heart disease is present (1). In addition to a complete history and physical examination, all patients should receive a 12-lead electrocardiogram (ECG), 2-dimensional echocardiogram, and exercise testing if they have an intermediate or more chance of having coronary heart disease (1). The ECG can also be useful to identify various ion channel abnormalities such as long QT syndrome (LQTS) associated with sudden cardiac death (SCD) in patients with no structural heart disease (1). Coronary angiography can be useful to exclude coronary heart disease in patients with life-threatening VAs such as polymorphic ventricular tachycardia (PMVT) (1). Cardiovascular magnetic resonance imaging may be appropriate if echocardiography does not provide an accurate assessment of ventricular function, e.g., in arrhythmogenic right ventricular cardiomyopathy/dysplasia or sarcoidosis (1-5).

The overwhelming majority of VAs in patients without structural heart disease carry an excellent prognosis, and

include premature ventricular complexes (PVCs), nonsustained VT, repetitive monomorphic VT, and sustained monomorphic VT. A small minority of patients may be prone to life-threatening rapid PMVT and ventricular fibrillation (VF). These mostly occur with the genetic arrhythmic syndromes or idiopathic VF (Table 1). This review will cover the clinical features and management options for patients without structural heart disease who have benign and potentially lethal VAs.

### Non-Life-Threatening Ventricular Arrhythmias, Typically Monomorphic

**General considerations.** The decision to suppress VAs that are not life-threatening depends on the severity of patient symptoms, but a potential additional reason may be to prevent a tachycardia-related cardiomyopathy (TCM) (6-11). Tachycardia-related cardiomyopathy has occurred with very frequent runs of VT as well as PVCs, although why PVCs alone cause it is not clear. The threshold of ectopy needed to result in TCM has been evaluated by many authors. Yarlagadda et al. (6) demonstrated in patients with >17,000 ectopic beats daily that successful ablation of ectopy resulted in improvement of ventricular function. Takemoto et al. (7) used the cutoff of PVC counts of >20% total heartbeats over 24 h; Baman et al. (11) had a cutoff value >24% PVC burden daily; Hasdemir et al. (10) used a

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**Abbreviations and Acronyms**

- ECG** = electrocardiogram
- ICD** = implantable cardioverter-defibrillator
- IVF** = idiopathic ventricular fibrillation
- LQTS** = long QT syndrome
- LVOT** = left ventricular outflow tract
- OTA** = outflow tract arrhythmias
- PMVT** = polymorphic ventricular tachycardia
- PVC** = premature ventricular complex
- RVOT** = right ventricular outflow tract
- SCD** = sudden cardiac death
- TCM** = tachycardia-related cardiomyopathy
- VA** = ventricular arrhythmia
- VF** = ventricular fibrillation
- VT** = ventricular tachycardia

PVC burden of 16% of daily heartbeats; and Niwano et al. (9) noted a cut-off of 31,268 PVCs per 24-h period. Thus, patients likely need to have >10,000 PVCs per day over a substantial period to cause TCM. Fortunately, TCM does not appear to be very common, and occurred in 6.8% of patients in 1 study (10) and only 13 of 239 patients presenting with frequent PVCs daily over a 4-year period had a significant reduction in left ventricular ejection fraction (9).

Because TCM develops in only a minority of patients with very frequent PVCs and nonsustained VT, it appears reasonable to withhold antiarrhythmic therapy in such patients who have minimal symptoms and to re-evaluate their ventricular function on a yearly basis or sooner if symptoms occur.

**Outflow tract VA.** Idiopathic VAs can originate in more than 1 area of the heart but are most common in the outflow tract area

(Table 1), nearly 80% of which originate from the right ventricular outflow tract (RVOT) (12). Other common outflow tract sites include left ventricular outflow tract (LVOT), the aortic sinuses of Valsalva, the area of aortomitral continuity, the superior basal septum near the His bundle, the pulmonary artery, and the epicardial surface of the outflow tracts (13–21).

**ANATOMIC CORRELATES.** The RVOT is leftward and anterior to the LVOT, and the pulmonic valve is superior to the aortic valve. The RVOT is a muscular infundibulum circumferentially whereas LVOT is part muscular and part fibrous. A large part of right and some part of left aortic sinuses of Valsalva overlie the muscular LVOT and are in close proximity to the atrioventricular node and His bundle. The VAs arising from these areas may show early activation near the His bundle region. The non-coronary cusp and posterior aspect of left coronary cusp are continuous with the fibrous aortomitral continuity, explaining the lack of VAs related to the non-coronary cusp. The VAs from the aortic sinuses of Valsalva arise from muscular extensions of the LVOT to areas above the base of the aortic valve cusps. These muscle fibers often exhibit slow conduction and fractionated electrograms. Localization of site of VA origin can be predicted using the QRS morphology on surface ECG, and the anatomic relationships help to explain the shared ECG patterns and subtle differences (Fig. 1) (22). The RVOT VAs present with a distinct ECG pattern of left

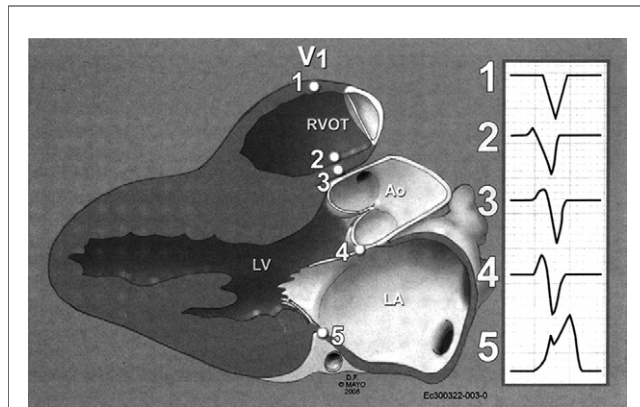
bundle branch block and inferior axis (Fig. 2) (23–26). In general, LVOT VAs manifest an early precordial R-wave transition (in V<sub>2</sub> or V<sub>3</sub>) because of its more posterior location compared with the RVOT (Fig. 3).

**ELECTROPHYSIOLOGIC MECHANISM.** It is well established that outflow tract arrhythmia (OTA) is due to triggered activity secondary to cyclic adenosine monophosphate-mediated delayed after depolarizations (23,24,27,28). Increased cyclic adenosine monophosphate due to beta-adrenergic receptor stimulation, for example, with exertion, results in release of calcium from the sarcoplasmic reticulum and delayed afterdepolarizations. Thus, the tachycardia may terminate with Valsalva maneuvers, adenosine, beta-adrenergic blockade, or calcium-channel blockers (12,27–29).

**CLINICAL FEATURES.** Typically, OTA occur between the ages of 20 and 40 years, and may have a slight female preponderance (30). Patients may be asymptomatic but often present with palpitations, chest pain, dyspnea, presyncope, and even syncope. In general, OTA occur more frequently with exertion or emotional stress, and may have a diurnal variation (31,32). Women may have an increase in symptoms related to changes in hormonal status (33). In general, the prognosis of truly idiopathic OTA is benign. Long-term follow-up studies have provided evidence that the vast majority of patients do not develop structural heart disease or SCD (34,35). However, as already noted, a small percentage of patients with very frequent VAs may have LV dysfunction over time, and rare reports have documented

**Table 1** Classification of Ventricular Arrhythmias in the Absence of Structural Heart Disease

|   |   |
|---|---|
| I. Non-life-threatening (typically monomorphic) |   |
| A. Outflow tract                                |   |
|   | Right ventricular outflow                             |
|   | Left ventricular outflow                              |
|   | Aortic sinus of Valsalva                              |
|   | Peri His bundle                                       |
| B. Idiopathic left ventricular tachycardia      |   |
|   | Left posterior fascicle                               |
|   | Left anterior fascicle                                |
|   | High septal fascicle                                  |
| C. Other  |   |
|   | Mitral annulus  |
|   | Tricuspid annulus                                     |
|   | Papillary muscle                                      |
|   | Perivascular epicardial                               |
| II. Life-threatening (typically polymorphic)    |   |
| A. Genetic syndromes                            |   |
|   | Long QT   |
|   | Brugada   |
|   | Catecholaminergic polymorphic ventricular tachycardia |
|   | Short QT  |
| B. Idiopathic ventricular fibrillation          |   |



**Figure 1** Correlation of Ventricular Ectopy Site of Origin With ECG Morphology

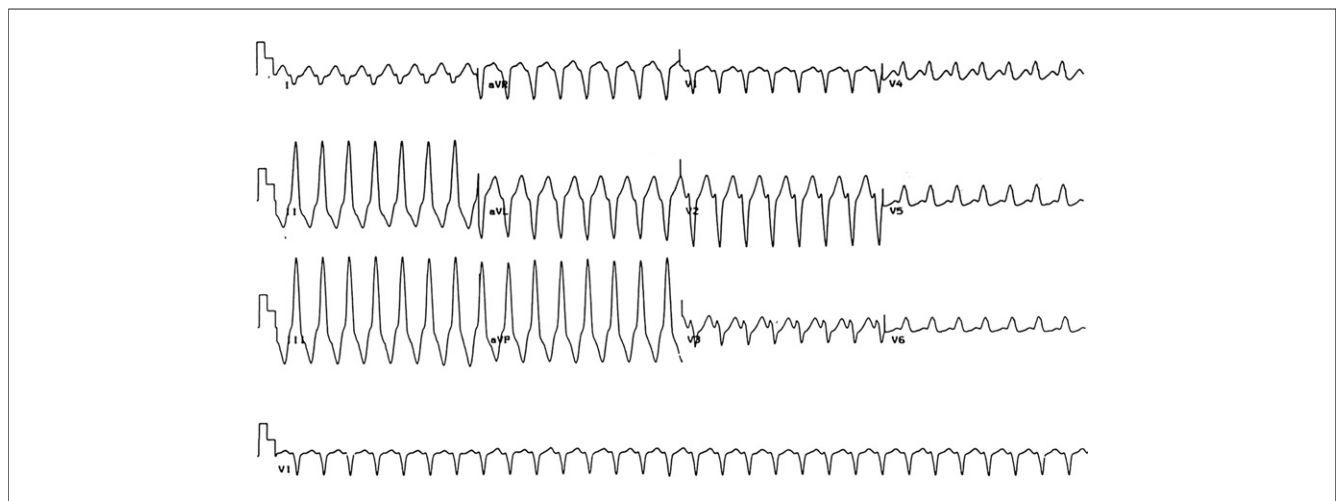
Correlation of the site of origin of ventricular ectopy with the electrocardiogram (ECG) morphology in  $V_1$ . The anatomy of the outflow tract region is such that areas on the right and left sides of the heart can be in close proximity to each other. This can give similar ECG patterns in several leads. However, note that in  $V_1$ , there is a gradual increase in the amplitude of the r-wave as the site of origin of the ventricular ectopy moves leftward. Ao = aorta; LA = left atrium; LV = left ventricle; RVOT = right ventricular outflow tract. Reproduced with permission from Asirvatham et al. (22).

cardiac arrest and PMVT in patients who were initially thought to have “benign” OTA (36–38). Viskin et al. (37) reported 3 such patients who exhibited a relatively short coupling interval (mean of 340 ms) of the PVCs. However, in a larger series, RVOT PVCs initiating VF or PMVT had a mean PVC coupling interval of  $409 \pm 62$  ms, clearly not “short” (36). These characteristics also seem to differ from the idiopathic VF patients reported by Haissaguerre et al. (39), who had very short-coupled ( $297 \pm 41$  ms) PVCs of Purkinje fiber origin. Unfortunately, there does not seem to

be a specific PVC coupling interval that predicts risk for a malignant VA.

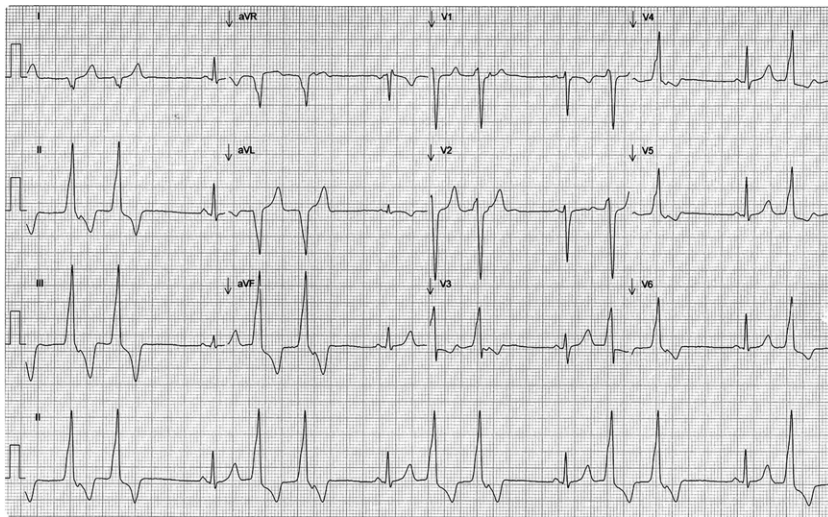
**TREATMENT.** Patients presenting in sustained VT may respond acutely to carotid sinus massage, Valsalva maneuvers, or intravenous adenosine or verapamil (40,41). Patients with no or minimal symptoms may be given reassurance without specific drug therapy. Long-term oral therapy with either beta-adrenergic blockers or calcium-channel blockers may control arrhythmias (40,42,43). Patients nonresponsive to beta-blockers and calcium-channel blockers may respond to class I or III antiarrhythmic agents (25,44). Radiofrequency catheter ablation may be considered in cases where medical therapy is ineffective or not tolerated. Multiple reports have shown excellent outcomes for ablation of OTAs by discrete radiofrequency lesions (7,13,14,16–20,45,46). Ablation of epicardial or aortic sinuses of Valsalva sites is also highly effective, but can be technically challenging and carries higher risks due to these sites’ proximity to coronary arteries.

**Idiopathic left VT.** Verapamil-sensitive idiopathic left ventricular tachycardias occur primarily due to re-entry involving the fascicles of the left bundle branch. Three varieties may occur: 1) left posterior fascicular VT with a right bundle branch block and left axis deviation on ECG; 2) left anterior fascicular VT with a right bundle branch block and right axis deviation; and 3) high septal fascicular VT with relatively narrow QRS complex and normal axis. Left posterior fascicular VT is the most common form (47–50) (Fig. 4). Patients are young, 15 to 40 years of age, and predominately men (>60%). It is usually paroxysmal, but incessant forms leading to a TCM have been described (51). In 1981, Belhassen et al. (52) observed that intravenous verapamil significantly slowed and often terminated this arrhythmia. In contrast



**Figure 2** 12-Lead ECG of RVOT Ventricular Tachycardia

On this 12-lead electrocardiogram (ECG) of right ventricular outflow tract (RVOT) ventricular tachycardia, note that there is a left bundle branch block pattern in the precordial leads with transition from a small r-wave to a large R-wave at  $V_3$  to  $V_4$ , consistent with a right-sided site of origin. Also consistent with the OT site is the inferior ECG axis.



**Figure 3** 12-Lead ECG of PVCs

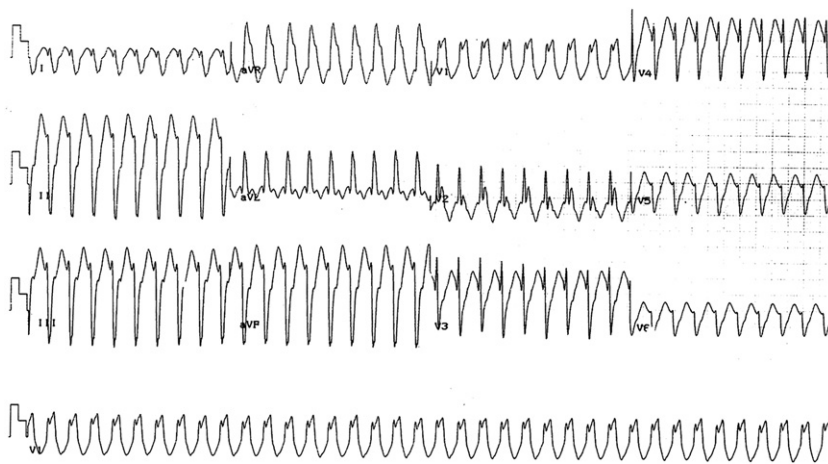
A 12-lead electrocardiogram (ECG) of premature ventricular contractions (PVCs) originating in the left coronary cusp/aortic sinus of Valsalva (ASV). Note that the QRS morphology in the limb leads is nearly the same as in the example in Figure 2. However, the precordial ECG leads are markedly different. There is a broad but small r-wave in  $V_1$  and  $V_2$ , and the transition from small to large R-wave is from  $V_2$  to  $V_3$ . Although that could still be from the right side, a left-sided site is more likely, and intracardiac mapping and ablation confirmed a left ASV site.

to its effect on OTA, adenosine usually has no effect on this tachycardia.

**ELECTROPHYSIOLOGIC MECHANISM.** Studies based on entrainment maneuvers have conclusively demonstrated a re-entrant mechanism (53–56). The re-entrant circuit is constituted by an orthodromic limb consisting of a zone of slow, decremental conduction in the intraventricular left septum proceeding from the base to the apex (55,56). The

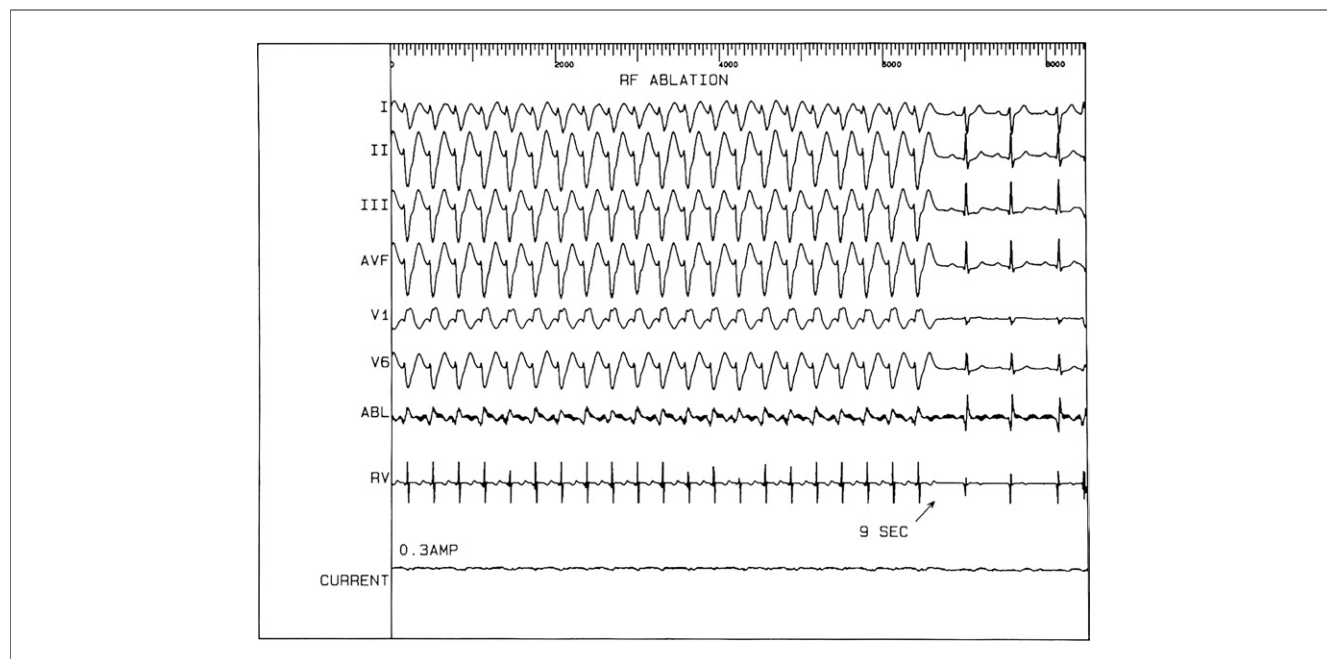
lower turnaround point is toward the apex, and the retrograde limb is formed by the Purkinje network.

**TREATMENT.** Intravenous verapamil slows and terminates the tachycardia by prolonging conduction in the decremental limb of the circuit (57,58). Several studies have also demonstrated long-term effectiveness of oral verapamil (59–61). As in the case of OTA, beta-blockers, and class I and III antiarrhythmic agents may be useful in some cases. Catheter ablation is an



**Figure 4** 12-Lead ECG of Idiopathic Left Ventricular Tachycardia

On this 12-lead electrocardiogram (ECG), note that there is a right bundle branch block pattern with a superior axis. This type of tachycardia has a site of origin near the left posterior fascicle.



**Figure 5 RF Catheter Ablation of Idiopathic Left VT**

Radiofrequency (RF) catheter ablation of idiopathic left ventricular tachycardia (VT): simultaneous tracings are electrocardiogram leads I, II, III, aVF, V<sub>1</sub>, and V<sub>6</sub>; intracardiac tracings from the ablation catheter near the left ventricle (LV) posterior fascicle (Abl) and at the right ventricle (RV) apex; and the energy delivery tracing (Current). Note that at 9 s after onset of 0.3 AMP, the tachycardia terminates. After this ablation, the VT was no longer inducible.

excellent option when medications are not tolerated or are ineffective (Fig. 5) (57,60,62–64). The most common approach during radiofrequency ablation involves the identification of the diastolic Purkinje potential during VT (62). In cases where VT is noninducible, ablation during sinus rhythm using electroanatomic mapping may be considered (64).

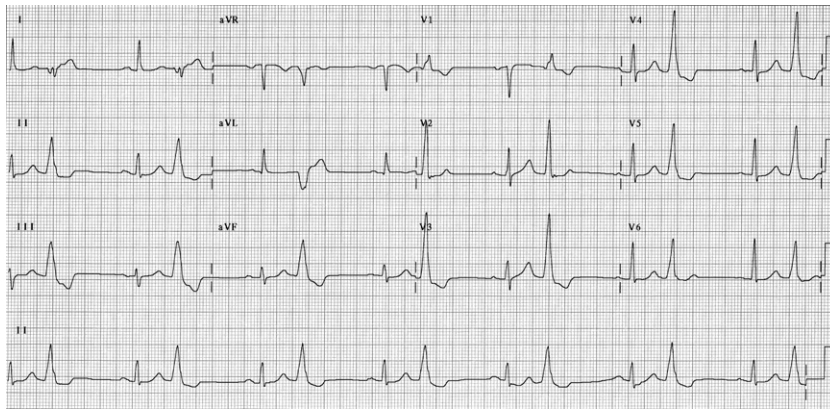
**Mitral annulus, tricuspid annulus, papillary muscle, perivascular epicardial ectopy.** Although OTA and fascicular VT form the vast majority of VA in patients with structurally normal hearts, ectopy may originate from any myocardial location. Certain sites such as the mitral annulus (65,66), tricuspid annulus (67), papillary muscles (68,69), and perivenous epicardial sites (70) show predilection. The ECG of the ventricular complexes originating from mitral annulus may show significant slurring of QRS complex onset resembling a delta-wave morphology seen in patients with ventricular pre-excitation (65,66). Epicardial foci of VAs are also characterized by a slurred QRS onset giving a pseudo-delta-wave appearance (Fig. 6). The slowed initial QRS activation was quantified by Daniels et al. (70), and a delayed precordial maximum deflection index  $\geq 0.55$  identified epicardial VTs with high specificity and sensitivity. The VAs from epicardial foci cluster along the major epicardial vasculature and show catecholamine and adenosine sensitivity.

### Life-Threatening Ventricular Arrhythmias, Typically Polymorphic

**Genetic syndromes with PMVT.** Long QT syndrome, catecholaminergic PMVT, Brugada syndrome, and short

QT syndrome are genetic syndromes that predispose to VAs and SCD (1), especially in young persons. Cardiac gross morphology and histology are normal, but abnormalities of ion channels or their regulatory proteins create an arrhythmogenic milieu. These conditions are rare, and taken together, have an estimated prevalence  $<5$  in 10,000 (1). Despite the diverse nature of these disorders, certain generalizations can be made. They may be inherited with incomplete penetrance and family history does not help to stratify risk of sudden death. The severity of ECG phenotype, presence of symptoms, and certain genotypes may predict increased risk. While implantable cardioverter-defibrillator (ICD) insertion is recommended for secondary prevention of cardiac arrest, primary prevention should be guided by risk stratification schemes and availability of effective medical treatment for a particular syndrome or genotype.

**Long QT syndrome.** The LQTS is characterized by abnormally prolonged QT intervals (corrected QT interval  $>440$  ms in men and  $>460$  ms in women) (71) with or without morphological abnormalities of the T waves (Fig. 7). A decrease in outward potassium currents or an increase in inward sodium currents prolongs the repolarization phase of the cardiac action potential, resulting in prolongation of the QT interval and predisposition to early afterdepolarizations and torsade de pointes VT. Twelve different genes involved in inherited LQTS have been described (72). The first 3—LQT1, LQT2, and LQT3—account for  $>90\%$  of the genotyped LQTS cases (73).



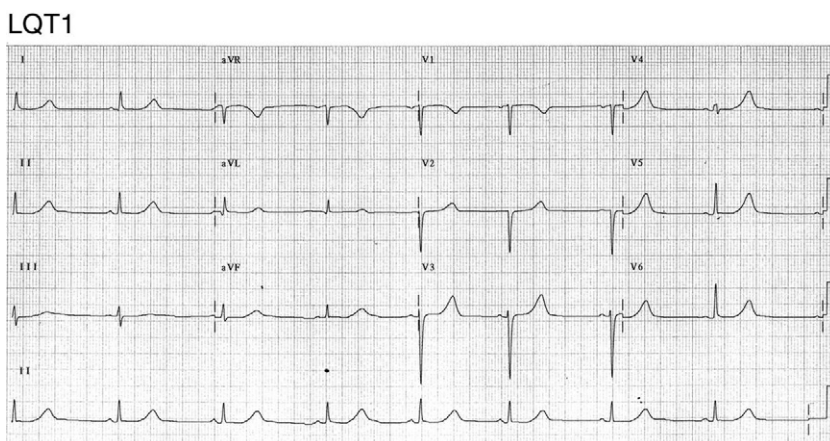
**Figure 6** 12-Lead ECG of PVCs Originating From LV Epicardium at Anterior Base

On this 12-lead electrocardiogram (ECG) of premature ventricular contractions (PVCs) originating from the left ventricular (LV) epicardium at the anterior base, the QRS complexes show right bundle branch block morphology in V<sub>1</sub> and upright R waves in ECG leads II, III, and aVF (inferior axis). Key is the broad, pseudodelta-wave appearance of the QRS complexes in the precordial leads that has been described with sites of origin on the mitral annulus and the ventricular epicardium. The site of origin was confirmed at mapping and ablation.

LQT1 and LQT2 are caused by mutations of *KCNQ1* and *KCNH2* genes that encode  $\alpha$  subunits of I<sub>Ks</sub> and I<sub>Kr</sub> potassium channels, respectively; LQT3 results from mutations of *SCN5A* gene that encode  $\alpha$  subunits of I<sub>Na</sub> sodium channels. The remainder involve mutations related to other channel subunits or their regulator proteins. Approximately 25% of affected patients may not have identifiable gene mutations (74,75).

The mean age of symptom onset is 12 years, and patients may present with syncope, seizures, or cardiac arrest. Clinical presentation and ECG repolarization (ST-T) patterns have been correlated to the genotype (76,77). Patients who have LQT1 often have broad-based T waves and frequently experience events during physical activity (especially swim-

ming). In LQT2, the T-wave is often notched in multiple leads. Triggers for LQT2 include startling auditory stimuli (e.g., from an alarm clock) and emotional upset. Patients who have LQT3 often demonstrate long ST segments. Most LQT3 events occur at rest or sleep. However, there is considerable overlap between LQTS genotype, the T-wave morphology, and the clinical presentation. The diagnosis of LQTS can be difficult, and the modified Schwartz score determines the clinical probability for having the condition on the basis of multiple data points including personal and family history, QT interval, and T-wave morphology (71). More recently, diagnostic evaluations such as response to exercise, epinephrine challenge, and genetic testing have also been utilized.



**Figure 7** 12-Lead ECG of LQTS

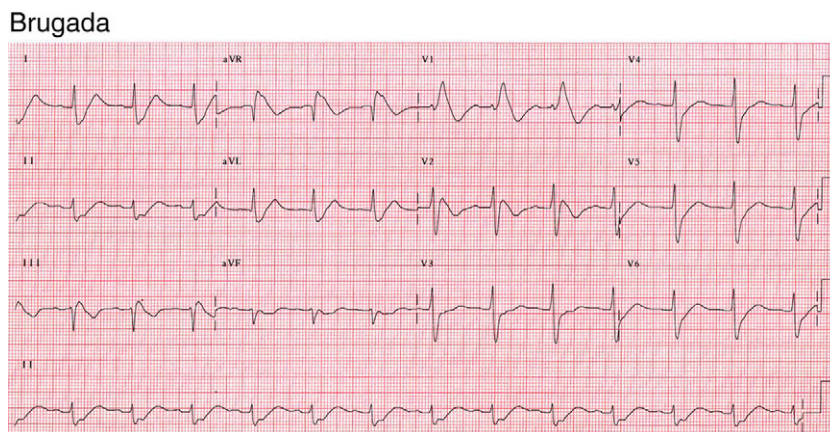
On this 12-lead electrocardiogram (ECG) of long QT syndrome (LQTS), the QT interval is 580 ms and the corrected QT interval is 513 ms. Genetic testing revealed a LQT1 syndrome.

The management of LQTS is complex. Preventive measures include avoidance of the trigger events and medications, including over-the-counter pills, that may further prolong QT interval. Risk stratification schemes based on the degree of QT prolongation, genotype, and sex have been developed (78). A corrected QT interval exceeding 500 ms poses a high risk for cardiac events. Patients who have LQT2 and LQT3 may be at higher risk for SCD compared with patients who have LQT1. Beta-blockers are indicated for all patients with syncope and for asymptomatic patients with significant QT prolongation (1). The role of beta-blockers in asymptomatic patients with normal or mildly prolonged QT intervals remains uncertain. Beta-blockers are highly effective in LQT1, but less effective in other LQTS (79,80). The role of beta-blockers in LQT3 is not established. Because LQT3 is a minority of all LQTS, symptomatic patients who have not undergone genotyping should receive beta-blocker therapy. Implantable cardioverter-defibrillators are indicated for secondary prevention of cardiac arrest and for patients with recurrent syncope despite beta-blocker therapy (1). Less defined therapies include gene-specific therapy with mexiletine (81), flecainide (82), or ranolazine (83) for some LQT3 patients, permanent pacing for bradycardia-dependent torsade de pointes, and surgical left cardiac sympathetic denervation for recurrent arrhythmias resistant to beta-blocker therapy (1,84). Catheter ablation of triggering PVCs has been reported to be successful in abolishing recurrent VT/VF in a few patients (85).

**Brugada syndrome.** The Brugada syndrome is characterized by coving ST-segment elevation in precordial leads V<sub>1</sub> to V<sub>3</sub> ( $\geq 2$  mm in 2 of these 3 leads are diagnostic), complete or incomplete right bundle branch block pattern, and clinical presentation with syncope or cardiac arrest (Fig. 8) (86,87). This pattern can be spontaneously present or provoked by sodium-channel-blocking agents such as aj-

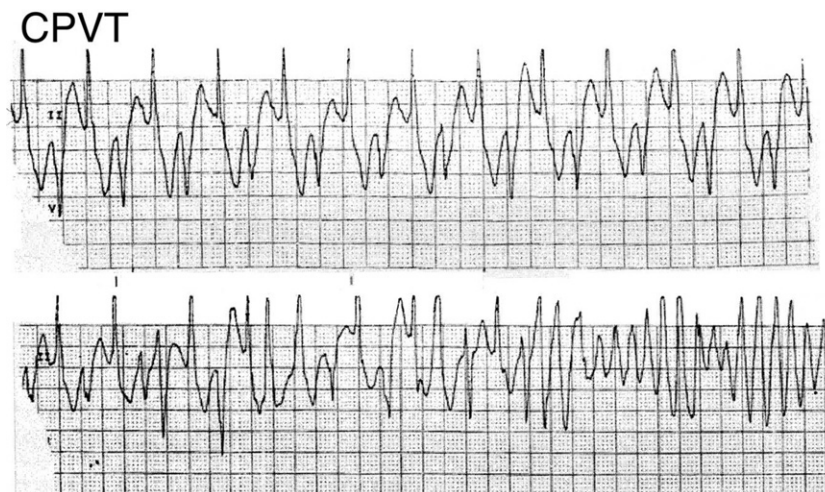
maline, flecainide, or procainamide (87). The syndrome manifests predominantly in men in the third and fourth decades of life. The typical ECG pattern can be transient and may only be detected during long-term ECG monitoring. Brugada syndrome has also been linked to SCD in young men in Southeast Asia and has several local names, including Lai Tai (“died during sleep”) in Thailand (88). Patients with Brugada syndrome are also prone to atrial fibrillation and sinus node dysfunction. Although 7 different genes involved in Brugada syndrome have been described, SCN5A gene mutations (BrS1) that lead to a loss of function of cardiac sodium channel (NaV 1.5) account for the vast majority of genotyped cases. However, even in patients with the typical Brugada syndrome ECG pattern, a positive genotype is obtained only a minority (13%) (89). BrS1 and LQT3 share SCN5A mutations as their basis, and overlapping phenotypes of Brugada syndrome and LQT3 have been reported (90,91).

There is no well-validated preventive medical therapy for Brugada syndrome, although quinidine has been proposed to play a role (92). Implantable cardioverter-defibrillators are effective in preventing sudden death and are indicated for cardiac arrest survivors (87). The major management dilemma arises in the decision to place prophylactically an ICD in a Brugada syndrome patient, based on the patient’s perceived risk of SCD. Patients with Brugada syndrome who have not had a cardiac arrest may be risk stratified on the basis of spontaneous ECG pattern and syncope (93). Patients with spontaneous ECG pattern and syncope are at high risk, and ICD insertion is generally recommended for primary prophylaxis (86,87). Asymptomatic patients without spontaneous ECG pattern are at low risk and may be followed up clinically. Asymptomatic patients with spontaneous ECG pattern are at intermediate risk, and their best therapeutic options may need to be individualized. Family history of SCD and specific genotypes do not predict events



**Figure 8** 12-Lead ECG of Brugada Syndrome

On this 12-lead electrocardiogram (ECG) of Brugada syndrome, note the coving of the ST-segment in the early precordial leads and right bundle branch block pattern.



**Figure 9** ECG Rhythm Strips of Child With CPVT

The electrocardiogram (ECG) rhythm strips of a 6-year-old girl with catecholaminergic polymorphic ventricular tachycardia (CPVT) are shown. The patient had a history of seizures with physical activity and was brought to the Emergency Department after such an episode, when the tracing was recorded. Bidirectional VT (**upper panel**) degenerated to ventricular fibrillation (**bottom panel**). Genetic testing uncovered a ryanidine-2 receptor defect. Figure provided by Len Steinberg, MD.

(93). Electrophysiology study for induction of VAs has inconsistent predictive value (94,95). Fragmented QRS interval has been reported to predict poor prognosis (96). Although no preventive medical therapy is available, low-dose quinidine may be used to treat frequent VAs in Brugada syndrome patients who already have an ICD (97), and quinidine and isoproterenol may be useful in patients having VT storms (98,99). Catheter ablation of triggering PVCs (85) and ablation of the RV outflow epicardial musculature (100) have been reported to be successful in abolishing recurrent VT/VF in a small number of patients. **Catecholaminergic PMVT.** Catecholaminergic PMVT is a disorder of myocardial calcium homeostasis, clinically manifested as exertional syncope and SCD due to exercise-induced VT that is often polymorphic or bidirectional (Fig. 9). The genetic basis is autosomal dominant, although autosomal recessive forms have been described more recently (101,102). The autosomal dominant form involves mutation of cardiac ryanodine receptor (RyR2 gene) in approximately 50% of patients (101,103). The autosomal recessive form, accounting for only 3% to 5% of genotyped cases, is due to mutations of the calsequestrin 2 gene (CASQ2). The ryanodine receptor spans the membrane of the sarcoplasmic reticulum and releases calcium triggered by calcium entry into the cell through L-type calcium channels. Calsequestrin is a protein that sequesters calcium ions within the sarcoplasmic reticulum. Both RyR2 and CASQ2 mutations cause intracellular calcium overload and delayed afterdepolarizations that form the basis of arrhythmogenesis in catecholaminergic PMVT.

The resting ECG is unremarkable, but the typical VT patterns are reproducible with exercise or catecholamine infusion. The VAs typically appear during sinus tachycardia

rates of 120 beats/min to 130 beats/min, with progressive frequency of PVCs followed by bursts of polymorphic or bidirectional VT (104). The mean age for presentation with syncope is  $7.8 \pm 4$  years (104). Electrophysiology study is not helpful in risk stratification. The mainstay of medical management is beta-blocker therapy, although as many as 46% may have recurrent events while receiving therapy (103,105). Calcium-channel blockers (106) may have limited effectiveness as adjunctive therapy. Flecainide blocks the RyR2 receptor and shows promise as a medical therapy, although prospective data are lacking (107,108). Because of the limitations of medical therapy, ICD insertion is appropriate for many patients who have had a cardiac arrest and for patients with life-threatening VA despite maximal medical therapy. Recurrent ICD shocks may occur, and an initial shock with its accompanying pain and anxiety may trigger further VAs. Surgical left cardiac sympathetic denervation may be used in resistant cases (109).

**Short QT syndrome.** Short QT syndrome is a rare disorder characterized by abnormally short QT intervals of <300 to 320 ms. The exact cutoff QT intervals for diagnosis are still debated, and diagnostic criteria involving corrected QT interval, clinical history, and genotyping have been proposed (110). The syndrome is associated with SCD and atrial fibrillation, and patients may present early in childhood. Mutations leading to gain of function of 3 genes encoding for repolarizing potassium currents (IKr, IKs, and IK1) have been associated with short QT syndrome. Only limited clinical experience has been reported, and the disease may be associated with a high incidence of SCD, leading many to recommend ICD implantation for secondary and primary prevention (111). Preliminary observations suggest quinidine might be useful (112).



## Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) presents as syncope or SCD in young people with normal hearts and no identifiable genetic syndrome. The events are typically unrelated to stress or activity, but may occur in clusters characterized by frequent ventricular ectopy and short episodes of VF or PMVT. The spontaneous VF or PMVT events are triggered by PVCs, generally with a short coupling interval, often referred to as “short coupled torsade.” The PVCs triggering the events may arise from the Purkinje fibers or the myocardium, and the former generally has shorter coupling intervals (see section, Outflow tract VA). Isoproterenol may be effective in suppressing VF storms in the acute setting, and quinidine may be useful on a long-term basis (113). Insertion of an ICD is recommended for all cases of IVF.

Haissaguerre et al. (39) described 27 patients who were resuscitated from recurrent IVF. Of the 24 patients with frequent PVCs, electrophysiologic mapping identified the PVCs originating from the RVOT in 4 patients and from the distal Purkinje system right ventricle or left ventricle in 20 patients. Catheter ablation eliminated the PVCs in all patients, and during a mean follow-up of  $24 \pm 28$  months, there was no recurrent VF in 24 of the 27 patients. Long-term follow-up of such patients (mean 63 months) also indicates excellent results from ablation of the triggering PVCs (114).

Early repolarization pattern, defined as elevated QRS-ST junction (J point) of at least 0.1 mV from baseline in the inferior or lateral ECG leads occurs more frequently in patients with IVF than in normal subjects (31% vs. 5%) (115). Such a pattern in the anterior precordial leads ( $V_1$  to  $V_3$ ) was excluded from the studies as it could occur in disease states such as Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia. Further, early repolarization pattern in the anterior precordial leads is considered to have a benign prognosis (116). Recent data suggest the *KCNJ8* gene may be involved in early repolarization syndrome (117). Early repolarization pattern is not uncommon and has for years been considered a normal ECG variant with a benign prognosis (116). The mechanism of VT or VF that can occur with it is not well understood (116). A recent study suggests the early repolarization with the ST segment showing a horizontal/descending pattern, but not the one with the ascending pattern, is associated with an increased risk for arrhythmic death (118). Still, the overall risk of SCD is very small. Until more is known about how to risk-stratify patients with the early repolarization syndrome, no specific work-up or therapy is recommended.

## Conclusions

Ventricular arrhythmias in structurally normal hearts are typically monomorphic with a benign prognosis. The usual

work-up to rule out structural heart disease includes an ECG and echocardiogram, but some patients may require cardiovascular magnetic resonance imaging or cardiac catheterization. If symptoms are mild, no therapy is usually necessary, but drugs—for example, beta-blockers or verapamil—or radiofrequency catheter ablation may be used for symptomatic patients. The genetic ion channelopathies and idiopathic VF present with PMVT that is potentially life-threatening. Such patients may require ICD therapy for secondary or primary prevention of SCD.

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**Key Words:** implantable cardioverter-defibrillator ■ structural heart disease ■ sudden cardiac death ■ ventricular fibrillation ■ ventricular tachycardia.