Ventricular Arrhythmias in the Absence of Structural Heart Disease

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Abstract

Ventricular arrhythmia (VA) in structurally normal hearts can be classified as monomorphic or polymorphic. Monomorphic VA is common and generally carries an excellent prognosis. However, rare sudden cardiac death events have been reported. Very frequent ventricular ectopic beats 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. Polymorphic ventricular tachycardia (VT) generally occurs in patients with genetic ion channel disorders including long QT syndrome, Brugada syndrome and catecholaminergic polymorphic VT. These arrhythmic syndromes are associated with sudden cardiac death. While the cardiac gross morphology is normal, suggesting a structurally normal heart, abnormalities exist at the molecular level and predispose them to arrhythmias. Finally, the early repolarization syndrome is associated with ventricular fibrillation episodes in the absence of structural heart disease or known channelopathies, and is characterised by the presence of J waves and ST-segment elevation in inferolateral leads.

Keywords

Idiopathic ventricular tachycardia • Idiopathic ventricular fibrillation • Outflow tract ventricular arrhythmias • Long QT syndrome • Brugada syndrome

Introduction

The evaluation and management of ventricular tachyarrhythmias are uniquely challenging due to the unpredictable and potentially lethal nature of the events. Malignant arrhythmias usually occur in the presence of significant structural heart disease (SHD). In this setting, ventricular arrhythmias carry a high risk of sudden cardiac death (SCD).

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Less commonly, ventricular tachycardia (VT) and ventricular fibrillation (VF) occur in hearts that appear normal. In many such cases, however, the heart is in fact not normal, but rather has less visible abnormalities including derangements of cardiac ion channels or structural proteins. In these patients, ventricular arrhythmias also carry a high risk of SCD. Thus, a significant majority of patients with VT or VF have some form of underlying cardiac disease, are at increased risk for SCD, and require a thorough cardiac evaluation to exclude structural abnormalities and nonstructural disorders.

Although the term idiopathic VT/VF is widely used for the VT/VF syndromes described in this chapter, use of "idiopathic" can be misleading. Historically, both VT and VF that occur in the absence of apparent heart disease have been referred to as idiopathic. However, with continual

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improvements in both the understanding of arrhythmia mechanisms and diagnostic methods, an increasing percentage of patients are now given a diagnosis (e.g., Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and catecholaminergic polymorphic VT). The diagnosis, characterization, and management of these VT/VF syndromes in the absence of SHD will be reviewed in this chapter.

Monomorphic VT in the Absence of Apparent SHD

Classification

Terminology and classifications vary, but most investigators acknowledge the existence of at least three syndromes of idiopathic monomorphic VT:

- Repetitive monomorphic VT, also called right ventricular (RV) outflow tract (OT) VT, is a triggered arrhythmia that is characterized by frequent short "salvos" of nonsustained VT. Less commonly, arrhythmias with similar characteristics and mechanisms originate from the LVOT, and these are considered a variant of RVOT.
- Paroxysmal sustained VT, which also arises from the RV, and is sometimes considered a sustained variant of repetitive monomorphic VT.
- Idiopathic left ventricular tachycardia, which differs from the LVOT variant of RVOT VT in both the mechanism (reentry) and site of origin (inferoapex or midseptum).

These three syndromes effectively characterize the majority of patients with idiopathic monomorphic VT and often unite clinical presentation, ECG morphology, and anatomic location into recognizable syndromes [1, 2].

Idiopathic VT has accounted for approximately 10% of all patients referred for evaluation of VT [1]. The mean age of patients with idiopathic VT is less than that of patients with VT secondary to underlying heart disease. It is important to recognize that not all VT that occurs in the apparent absence of structural heart disease is idiopathic VT. Distinguishing idiopathic VT from other monomorphic VT syndromes is important for several reasons:

- Idiopathic VT is generally considered to have an excellent prognosis in terms of freedom from both the development of structural heart disease and arrhythmic death [3–9]. There are several exceptions to this generalization, however, and episodes of SCD can occur.
- Idiopathic VT often responds to antiarrhythmic drugs that would be unhelpful or even contraindicated in VT occurring in the setting of coronary heart disease.
- Most idiopathic VT syndromes are now amenable to cure with catheter ablation techniques.

Diagnostic Evaluation

By definition, patients with idiopathic monomorphic VT have no detectable structural heart disease. Thus, the assessment of these patients focuses upon establishing the presence of a normal heart.

General Approach

- The resting ECG is typically normal between arrhythmia episodes, although some patients have temporary ECG repolarization abnormalities immediately after VT termination.
- The signal averaged ECG recorded during sinus rhythm is usually normal [5, 10].
- Functional studies of left ventricular (LV) and RV performance during sinus rhythm are normal, although segmental wall motion abnormalities may be seen immediately after VT termination. However, LV dysfunction can occur as a consequence of idiopathic VT, due to a tachycardia-induced cardiomyopathy. Such a myopathy can develop without persistent tachycardia if there are very frequent PVCs (i.e., >20,000 per day). This is a very important condition to recognize, as the LV dysfunction is reversible with treatment of the arrhythmia [11].
- The exercise stress test should be normal. Coronary angiography should also be normal.
- Cardiovascular magnetic resonance imaging (CMR) may reveal mild structural abnormalities of the RV in patients with RMVT, primarily involving the free wall (focal thinning, fatty infiltration, and wall motion abnormalities). The significance of these changes is unclear, since there is a poor correlation between the origin of the RMVT and the site of the CMR abnormalities unless they are also present in the RVOT.
- RV biopsy, which is rarely performed, is usually normal, although a number of studies have reported abnormalities that are nonspecific and of no significant value [12].

Repetitive Monomorphic VT

Repetitive monomorphic VT (RMVT) is characterized by frequent short "salvos" of monomorphic nonsustained VT [13]. Although RMVT is considered to occur in "normal" hearts, magnetic resonance imaging often reveal mild structural abnormalities of the RV, primarily involving the free wall (focal thinning, fatty infiltration, and wall motion abnormalities) [14]. The functional significance of these changes is uncertain. In the few cases studied, DNA from myocardial biopsies of ventricular muscle has been normal [15].

Epidemiology and Clinical Features

RMVT occurs almost exclusively in young to middle-aged patients without structural heart disease [1–8]. A surprising number of competitive athletes (particularly cyclists) are identified in many series of RMVT.

The most common associated symptoms are palpitations and lightheadedness during episodes. Most arrhythmias are nonsustained, but up to one-half of patients have some sustained episodes, and some patients have only sustained VT. Bursts of nonsustained VT are typically provoked by emotional stress or exercise, often occurring during the "warm-down" period after exercise, a time when circulating catecholamines are at peak levels [4–7]. There may also be a circadian pattern, with prominent peaks between 7 and 11 AM and 4 and 8 PM, correlating with periods of increased sympathetic activity [16]. In some patients, a critical "window" of heart rates (upper and lower thresholds) that result in occurrence of the arrhythmia can be defined.

The inducibility of RMVT by stress or catecholamine infusion is suggestive of an abnormality in cardiac sympathetic function. Consistent with this hypothesis is evidence of regional cardiac sympathetic denervation in some patients with RMVT and structurally normal hearts.

Site of Origin

The ouflow tract (OT) regions have complex three-dimensional anatomic relationships, which make the recognition of the ventricular arrhythmia origin particularly challenging. Different electrocardiographic algorithms have been proposed to predict LVOT vs RVOT origin of OT-VAs [17–22]. However, their accuracy has been recently questioned, especially when the transition in the precordial leads occurs in V3 [23] and/or the maximum electrogram (EG) precocity is located in the septal RVOT [24].

The most frequent site of origin of idiopathic VT described in literature is the RV outflow tract. However, sites of origin have been also recognised in the RV inflow tract, the free wall of the RVOT, the root of the pulmonary artery, the left and right aortic sinus of Valsalva, the left ventricle, the mitral annulus, and the papillary muscles.

Electrocardiographic Features

(a) RVOT. The majority of RMVT episodes have a characteristic ECG appearance with left bundle branch block, inferior axis and late precordial transition (>V3) (Fig. 17.1).

(b) LV outflow tract. Two different patterns may be observed:
- A right bundle, inferior axis morphology with a monophasic R wave in V1 that arose from the left fibrous trigone.
- A pattern similar to typical RMVT from the RVOT (left bundle, inferior axis) except that the precordial transition was earlier (at V2 for the LVOT as compared to V3 or later for the RVOT).

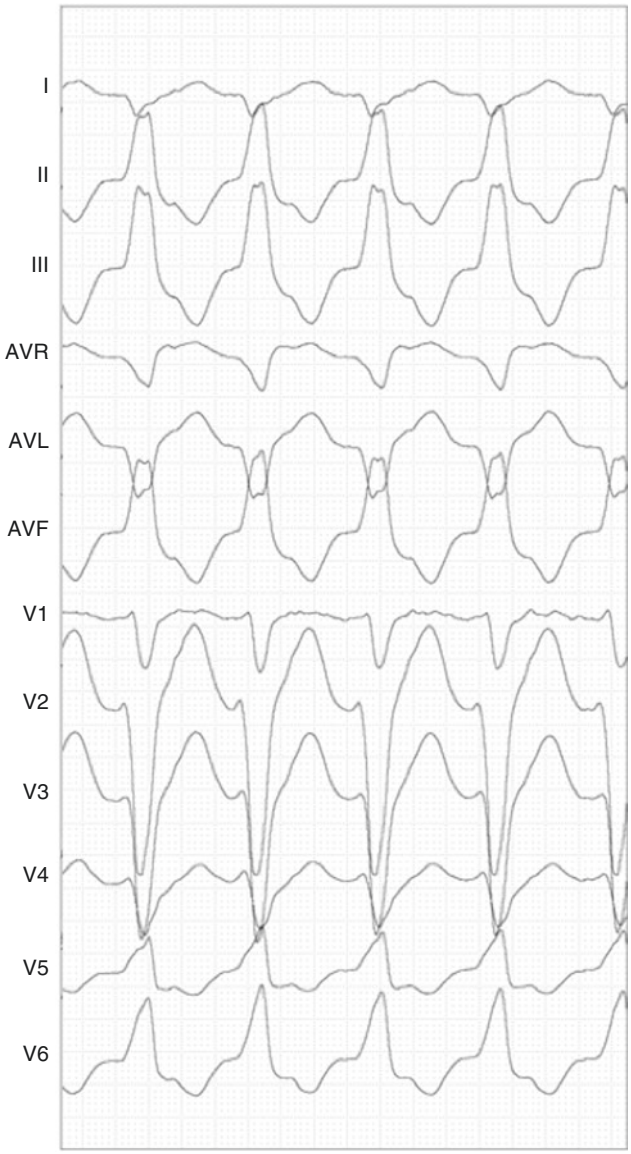

Fig. 17.1 Example of right ventricular outflow tract tachycardia

Although there is some interindividual variability, ventricular premature complexes arising from the left aortic sinus tend to be negative in lead I and have a "w" pattern in V1, while ventricular premature complexes with a broad R wave in V1 is characteristic of a right aortic cusp origin [19].

Electrophysiologic Features

RMVT can be induced in the EP laboratory, although usually not with programmed stimulation [4, 5]. In most patients, sustained or nonsustained episodes occur in response to burst atrial or ventricular pacing, and are greatly facilitated by isoproterenol or epinephrine infusion. These electrophysiologic observations suggest that triggered activity due to delayed afterpotentials, rather than reentry, is the

mechanism of RMVT. The response to "pharmacologic probes" further strengthens this hypothesis. RMVT has been terminated with adenosine, verapamil and beta blockers, all of which interfere with the cAMP-mediated slow inward calcium current. These observations are consistent with the hypothesis that RMVT results from triggered activity induced by cAMP-mediated delayed after depolarizations (DADs) [25]. However, the lack of specificity of these probes and the absence of a uniform response supports the general consensus that the mechanism of RMVT is incompletely characterized and may vary among individuals. Additional support for other mechanisms is based upon the observation that the tachycardia may, in some patients, terminate with overdrive pacing, ventricular extrastimulation, or autonomic modulation using Valsalva maneuver or carotid sinus pressure.

Prognosis

The prognosis of RMVT is almost uniformly good [26]. However, more recent studies in which these other syndromes were unlikely have identified a malignant variant of RMVT. Polymorphic VT and VF, which are malignant arrhythmias, have been demonstrated in patients with RMVT [27–29]. In these patients, VPBs are more closely coupled to prior beats than is usual for RMVT [27]. It was postulated that relatively early triggered beats occurred in a vulnerable period during repolarization, resulting in VF.

Medical Therapy

Medical therapy serves two roles in RMVT: termination of the arrhythmia; and prevention of recurrence. RMVT can be terminated with adenosine, verapamil and beta blockers, all of which interfere with the cAMP-mediated slow inward calcium current. For prevention of recurrence, verapamil and beta blockers are often used as first-line agents. In those cases refractory to verapamil and beta blockers, the combination of a beta blocker with a class I drug may be useful.

Radiofrequency Ablation

There has been increasing use of radiofrequency (RF) ablation in patients with symptomatic RMVT. Success rates for RF catheter ablation range from 80 to 100% [30–34]. The success rate depends in part upon the location of the focus; the success of catheter ablation for idiopathic VTs in atypical positions is generally not as high as for RVOT locations [31]. Radiofrequency ablation is generally associated with a low rate of procedural complications. However, recent studies have shown that a significant proportion of patients may present VT recurrence during long-term follow up, although with a lower burden [35]. The likelihood of successful ablation may be less when the site of origin is not endocardial or not definitively identified during mapping.

Idiopathic Left Ventricular Tachycardia (ILVT)

Belhassen was the first to report the characteristic termination of this VT with intravenous verapamil [36], accounting for its two descriptive eponyms: Belhassen VT; and verapamil-responsive VT.

Clinical Features

The typical patient with ILVT presents at age 20–40, but often reports symptomatic episodes dating back to adolescence. The clinical characteristics of ILVT appear to be more uniform than those of the idiopathic RV tachycardias [9, 36].

- It has a more variable association with physical activity, and is not usually provoked by exercise.
- It frequently produces symptoms such as palpitations and presyncope; syncope is uncommon.
- Cardiac arrest is rare, but isolated cases have been reported.
- Tachycardia-related cardiomyopathy has been reported, but is unusual since episodes are typically infrequent.

Site of Origin

Endocardial mapping during the VT demonstrates that the site of earliest activation is the inferoseptal region of the left ventricle in patients with a left frontal axis [9]. Mapping for catheter ablation also consistently localizes this VT to the inferior aspect of the midseptal region. In comparison, the anterosuperior left ventricle is the initial site in those patients with VT that has a right frontal axis.

Electrocardiographic Features

Corresponding to its left ventricular origin, ILVT has a right bundle branch block morphology with a left superior frontal plane axis and a relatively narrow QRS duration (typically 0.12–0.14 s). A small subset of patients with ILVT has a right frontal plane. ILVT is often confused with supraventricular tachycardia because of its characteristic ECG morphology, and the response to verapamil (Fig. 17.2).

Electrophysiologic Features

ILVT is typically reproduced in the electrophysiology laboratory using programmed stimulation employing extrastimuli and, on occasion, with rapid atrial or ventricular pacing. In contrast to RMVT, ILVT is not usually provoked by isoproterenol infusion.

The His bundle is commonly activated early in a retrograde fashion during ILVT, and a distinct Purkinje spike typically precedes the onset of the QRS. However, the retrograde His bundle deflection can be dissociated from the QRS complex by premature stimulation in the ventricle, atrium, or His region, implying that the reentrant circuit does not require the His bundle. These findings also suggest that the

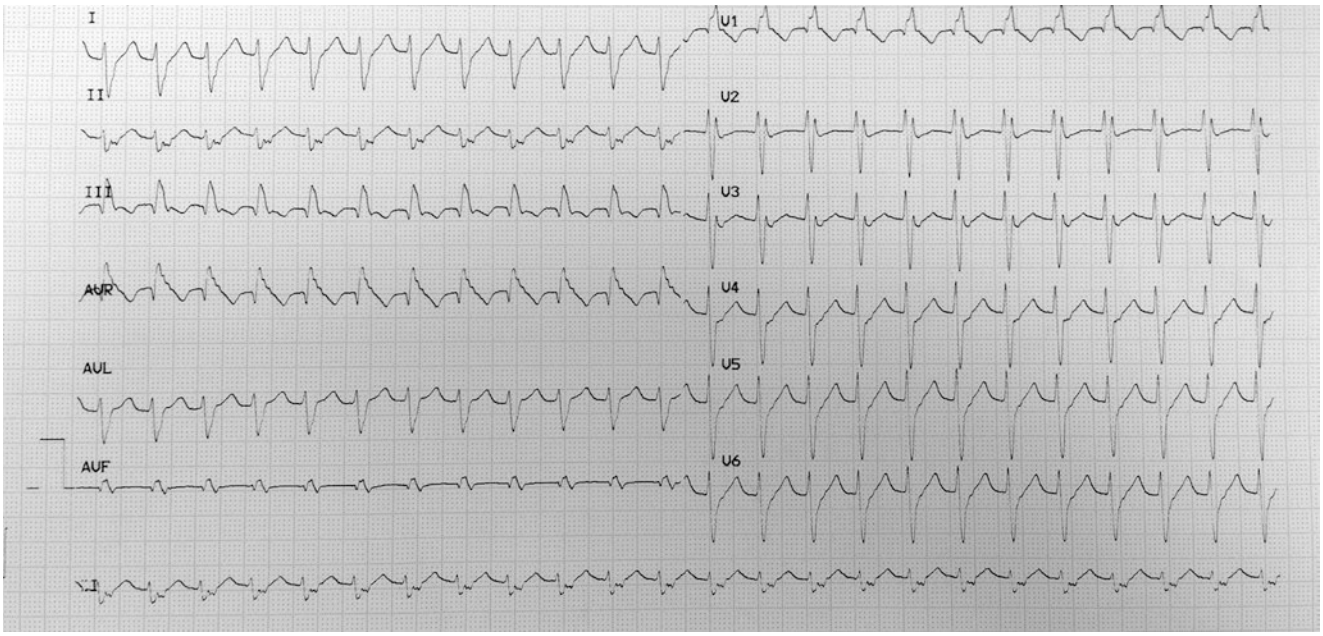

Fig. 17.2 Electrocardiographic pattern of fascicular tachycardia

posterior fascicle of the left bundle branch may be a part of, or at least in close proximity to the VT circuit. The terms fascicular ventricular tachycardia and fascicular tachycardia have been used to describe this arrhythmia.

Treatment of ILVT

Verapamil is usually effective in the treatment of ILVT, both for the termination of acute episodes and the prevention of recurrence. Catheter ablation has been performed with efficacy rates of 85–100% in patients with resistant or incessant ILVT or those intolerant of medications. Selection of ablation target sites focuses on pace mapping techniques and/or activation mapping, with particular attention to the mid-diastolic potential and/or presystolic Purkinje activation [37, 38].

Polimorphic VT and VF in the Absence of Apparent SHD

In addition to monomorphic VT, both polymorphic VT and VF can occur in the absence of structural heart disease. In contrast to the generally good prognosis associated with idiopathic monomorphic VT, these syndromes are associated with an increased risk of SCD.

Congenital Long QT Syndrome (LQTS)

The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) and an increased risk of sudden cardiac death [39]. This syndrome is associated with an increased risk of a characteristic life-threatening polymorphic ventricular tachycardia known as torsades de pointes [40].

While mutations in numerous genes have been identified in patients with congenital LQTS, two clinical phenotypes have been described that differ in the type of inheritance and the presence or absence of sensorineural hearing loss: the more common autosomal dominant form, the Romano-Ward syndrome, has a purely cardiac phenotype. On the other hand, the autosomal recessive form, the Jervell and Lange-Nielsen syndrome, is associated with LQTS and sensorineural deafness, and a more malignant clinical course.

Epidemiology

Although it is difficult to determine accurately, the incidence of congenital LQTS has been estimated between 1 in 2500 and 1 in 7000 in the general population [41].

Clinical Manifestations

The clinical manifestations of congenital LQTS are highly variable. Many patients have no symptoms, while symptoms (generally resulting from an arrhythmia) can range from palpitations to sudden cardiac death. Patients without symptoms typically come to medical attention because they have an affected family member or a prolonged QTc is identified on an electrocardiogram obtained for some other reason. Patients with arrhythmias may present with palpitations, presyncope, syncope, or sudden cardiac arrest. Many times the arrhythmias are transient or self-terminating, resulting in palpitations or presyncope. Patients may present with

syncope or sudden cardiac arrest if the arrhythmia is sustained or results in hemodynamic collapse.

Patients with LQTS frequently present with syncope and/or an apparent seizure due to an arrhythmia, typically polymorphic VT. Syncopal episodes associated with ventricular arrhythmias due to LQTS may have tonic-clonic movements and may be misdiagnosed as a primary seizure disorder. Distinguishing between a primary seizure disorder and seizures secondary to LQTS may be challenging, and the entities may overlap. In addition, patients with epilepsy and a recent seizure (within the preceding 2 years) as well as patients who are taking anti-epileptic medications with sodium channel blocker properties (e.g., phenytoin, carbamazepine, gabapentine, etc) appear to have an increased risk of sudden cardiac death. A screening ECG should be performed in all patients following a first afebrile seizure or unexplained syncope, including episodes consistent with neurocardiogenic (vasovagal) syncope. Those with borderline or prolonged QT intervals should be referred to a cardiologist for further evaluation. Emotional stress or physical exertion preceding syncope or seizure may suggest the possibility of LQTS-associated arrhythmia.

The majority of arrhythmias in patients with congenital LQTS are ventricular tachyarrhythmias, although bradycardia, atrioventricular block, and atrial arrhythmias are present in a minority of patients.

The classic arrhythmia associated with LQTS is a form of polymorphic VT called torsades de pointes. Polymorphic VT is defined as a ventricular rhythm faster than 100 beats per minute with frequent variations of the QRS axis, morphology, or both [42]. In the specific case of torsades de pointes, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to "twist" around the isoelectric line of the recording, hence the name torsades de pointes.

Arrhythmias in patients with LQTS are frequently triggered by external events (e.g., noise, exercise, stress, etc.) and are often pause dependent (the beat triggering the arrhythmia is preceded by an ectopic beat and a subsequent pause). In addition, factors that contribute to the development of acquired LQTS, such as medications known to prolong the QT interval and electrolyte disturbances, can provoke arrhythmias in patients with congenital LQTS which is "mild" or previously unknown to the patient.

While over one dozen genotypes have been described, the great majority of cases of LQTS are accounted for by three genotypes: LQT1 (40–55%), LQT2 (35–45%), and LQT3 (8–10%). There is an association between the triggers that initiate arrhythmic events and the specific genotype of LQTS [43]. Arrhythmic events in patients with LQT1 are most often related to exercise. Acute arousal events (such as exercise, emotion, or noise) are much more likely triggers in LQT1 and LQT2 than LQT3 [35]. Events triggered by auditory stimuli, such as an alarm clock or telephone ringing, are most typically seen in LQT2 [44]. Pause-dependent torsades de pointes is common among patients with LQT2, but rare in patients with LQT1. Patients with LQT2 and LQT3 are at highest risk of events when at rest or asleep (68% of events), compared with LQT1 in which only 3% of events occurred at rest or when asleep.

Diagnosis

The diagnostic approach to LQTS includes evaluation of the specific clinical setting (cardiac event, asymptomatic family member, or incidentally discovered QT prolongation) and assessment of the ECG features described above.

LQTS score: A weighted scoring system for the diagnosis of congenital LQTS, also called the Schwartz score, incorporates the measured QTc interval and other clinical and historical factors [43]. An algorithm was developed in which diagnostic criteria were assigned points (Table 17.1).

The points are added to calculate the LQTS score. The probability of having LQTS is rated as low, intermediate, or high for scores of ≤1, 1.5 to 3, and ≥3.5, respectively.

Exercise testing. In most children and young adults, the QT interval shortens with exercise and increased heart rate. In contrast, in individuals with LQT1 or LQT2, the QT interval may fail to shorten or may lengthen with exertion and higher heart rates and may be prolonged during the recovery phase after exercise.

In some patients, the diagnosis of LQTS may be uncertain after application of the diagnostic criteria outlined above.

Table 17.1 Schwartz score for LQTS diagnosis

Diagnostic criteria	Points
ECG findings	
Corrected QT intervalo (ms)	
≥480	3
460–470	2
450–460	1
Corrected QT at 4th minute after stress test ≥480 ms	1
Torsade de pointes (in the absence of drugs that prolong QT)	2
T-wave alternans	1
Notched T wave in three leads	1
Resting heart rate below second percentile for age (restricted to children)	0.5
Clinical findings	
Syncope	
With stress	2
Without stress	1
Family history	
Family members with LQTS	1
Unexplained SCD in immediate family members <30 years of age	0.5

Additional testing, including ambulatory monitoring or drug testing, may be helpful in such patients.

Drug testing. Evaluation of the QT interval after provocative testing with drugs may help differentiate patients with suspected LQTS from normal patients, and among those with LQTS may distinguish one genetic defect from another. The most commonly used drugs are beta-adrenergic agonists, such as isoproterenol and epinephrine.

Treatment

Cuurent guidelines recommend [45]:

- Lifestyle modification is recommended for all patients with either a clinical or genetic diagnosis of LQTS: avoidance of drugs that prolong the QT interval or reduce the serum concentrations of potassium or magnesium; avoidance of competitive sports or strenuous activity.
- Beta blocker therapy is recommended for patients with QT prolongation and suggested for patients with a molecular diagnosis of congenital LQTS but a normal QT interval.
- ICD implantation is recommended for survivors of a cardiac arrest who have a reasonable expectation of survival with a good functional status for at least 1 year.
- ICD implantation is suggested for patients who experience sustained VT and/or a syncopal event consistent with a tachyarrhythmia while on beta blocker therapy.
- Beta blocker therapy should be initiated or continued in all patients who receive an ICD.

Brugada Syndrome

The Brugada syndrome is an autosomal dominant genetic disorder with variable expression characterized by abnormal findings on the surface electrocardiogram in conjunction with an increased risk of ventricular tachyarrhythmias and sudden cardiac death. Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1–V3 [46].

Two terms, distinguished by the presence or absence of symptoms, have been used. Patients with typical ECG features who are asymptomatic and have no other clinical criteria are said to have the **Brugada pattern**. Patients with typical ECG features who have experienced sudden cardiac death or a sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have the **Brugada syndrome**.

Pathogenesis

Genetics. Genetic analysis has led to the identification of causative mutations in the SCN genes SCN5A and SCN10A, encoding subunits of a cardiac sodium channel.

Sodium channel genes. The defective myocardial sodium channels reduce sodium inflow currents, thereby reducing the duration of normal action potentials. In the right ventricular outflow tract epicardium, there is a prominent transient outward current, called I(to), which causes marked shortening of the action potential in the setting of reduced sodium inflow [47].

The relationship between sodium channel abnormalities and ST segment elevation is not fully understood. The ventricular myocardium is composed of at least three electrophysiologically distinct cell types: epicardial, endocardial, and M cells. The ST segment elevation and T wave inversions seen in the right precordial leads in Brugada syndrome are thought to be due to an alteration in the action potential in the epicardial and possibly the M cells, but not the endocardial cells [47]. The resulting dispersion of repolarization across the ventricular wall, which on noninvasive electrocardiogram mapping is isolated in the RV outflow tract, results in a transmural voltage gradient that is manifested in the electrocardiogram as ST segment elevation [48]. In addition, noninvasive ECG mapping has also shown evidence of an arrhythmogenic substrate in the RV outflow tract with delayed activation, slow conduction, and steep repolarization gradients between the RV outflow tract and the rest of the right ventricle [48]. This substrate may predispose to local reentry and ventricular arrhythmias.

SCN5A. Mutations in SCN5A, have been found in 18–30% of families with Brugada syndrome [49, 50]. The SCN5A mutations seen in Brugada syndrome are "loss of function" mutations and result in a variety of abnormalities in sodium channel activity including failure of expression, alterations in the voltage and time dependence of activation, and accelerated or prolonged recovery from inactivation. In addition, mutations may explain the ability of sodium channel blockers to expose the ECG changes in some patients with this disorder [49].

SCN10A. Mutations in SCN10A have been reported in 17% of Brugada syndrome probands, which is comparable to the 20 percent of probands found to have SCN5A mutations [51]. Coexpression of the mutant SCN10A gene with wild-type SCN5A causes a major loss of function of the sodium channel, with reduced current and slower recovery from inactivation. A longer PR interval, longer QS duration, and higher incidence of ventricular tachyarrhythmias and sudden death were noted in patients carrying mutations of SCN10A compared with gene-negative patients with Brugada syndrome.

Ventricular arrhythmias and phase two reentry. Ventricular arrhythmias may result from the heterogeneity of myocardial refractory periods in the RV. This heterogeneity arises from the presence of both normal and abnormal sodium channels in the same tissue, and from the

differential impact of the sodium current in the three layers of the myocardium. Within the epicardium, the juxtaposition of myocytes with different refractory periods can produce the triggers that initiate sustained arrhythmias via a unique type of reentry called phase two reentry. In cardiac myocytes with defective sodium channels, initial depolarization is blunted (phase zero), and the counterbalancing effect of I(to) (phase 1) may be more significant. This phenomenon is more dramatic in the RV outflow tract epicardium where I(to) currents are greater. In combination, this results in less initial depolarization and reduced activation of the calcium channels that maintain the depolarized state during phase two. Thus, phase two of the cardiac action potential can be dramatically shortened. The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction block. However, due to the abbreviation of phase two, these same cells have a much shorter refractory period and recover excitability before the surrounding cells. The combination of localized conduction block and a shortened refractory period provides the substrate for localized reentry, which, in this case, is referred to as phase two reentry. The closely-coupled ventricular premature beats that result from phase two reentry may precipitate sustained ventricular arrhythmias [52].

Autonomic tone. An imbalance between sympathetic and parasympathetic tone may be important in the pathogenesis of Brugada syndrome, as suggested by the nocturnal occurrence of the associated tachyarrhythmias and the alteration of typical ECG changes by pharmacologic modulation of autonomic tone [53–55].

Fever. Data from a retrospective review of 111 patients with Brugada syndrome suggest that fever is a trigger for ECG changes and cardiac arrest [56]. In patients with possible Brugada syndrome, obtaining an ECG during a febrile illness can be useful.

Clinical Features

Most clinical manifestations of the Brugada syndrome are related to life-threatening ventricular arrhythmias. Sudden cardiac arrest may be the initial presentation of Brugada syndrome in as many as one-third of patients. Patients may also present with an episode of syncope with features suggestive of a tachyarrhythmic cause of the syncope. Palpitations related to ventricular tachyarrhythmia are not common in the Brugada syndrome, but patients may present with palpitations related to atrial fibrillation, which is associated with Brugada syndrome and may be the first presentation of the disease. Nocturnal agonal respiration is also described and is part of the diagnostic criteria.

ECG Patterns

There are two distinct patterns of ST elevation [57]:

- Type 1 ECG (coved type): the elevated ST segment (≥2 mm) descends with an upward convexity to an inverted T wave (Fig. 17.3).
- Type 2 pattern: the ST segment has a "saddle back" ST-T wave configuration, in which the elevated ST segment descends toward the baseline, then rises again to an upright or biphasic T wave.

Moving the right precordial chest leads superiorly to the second or third intercostal space may increase the sensitivity of detecting these abnormalities and should be performed when there is a doubt about the diagnosis.

Diagnosis

*Diagnostic criteria. D*iagnostic criteria have been proposed by professional societies from both Europe and North America [58]. In practice, most patients are diagnosed using the following diagnostic criteria:

- Appearance of type 1 ST segment elevation (coved type) in more than one right precordial lead (V1–V3) in the presence or absence of a sodium channel blocker, plus at least one of the following:
- Documented ventricular fibrillation
- Polymorphic ventricular tachycardia (VT)
- Family history of sudden cardiac death at less than 45 years of age
- Family history of type 1 Brugada pattern ECG changes
- Inducible VT during electrophysiology study
- Unexplained syncope suggestive of a tachyarrhythmia
- Nocturnal agonal respiration

Diagnostic Testing and Risk Stratification

Once the diagnosis of Brugada syndrome is suspected based on the clinical presentation and electrocardiogram findings, additional testing may be considered to further confirm the diagnosis of Brugada syndrome and to provide an estimate of risk of ventricular arrhythmias and sudden cardiac death in the individual patient.

Drug challenge. Among patients with the type 2 Brugada ECG pattern, the type 1 Brugada ECG pattern can occasionally be unmasked by sodium channel blockers (flecainide, ajmaline or procainamide). The importance of unmasking the type 1 Brugada ECG pattern relates to its relevance in confirming the diagnosis of Brugada syndrome, particularly in patients without symptoms.

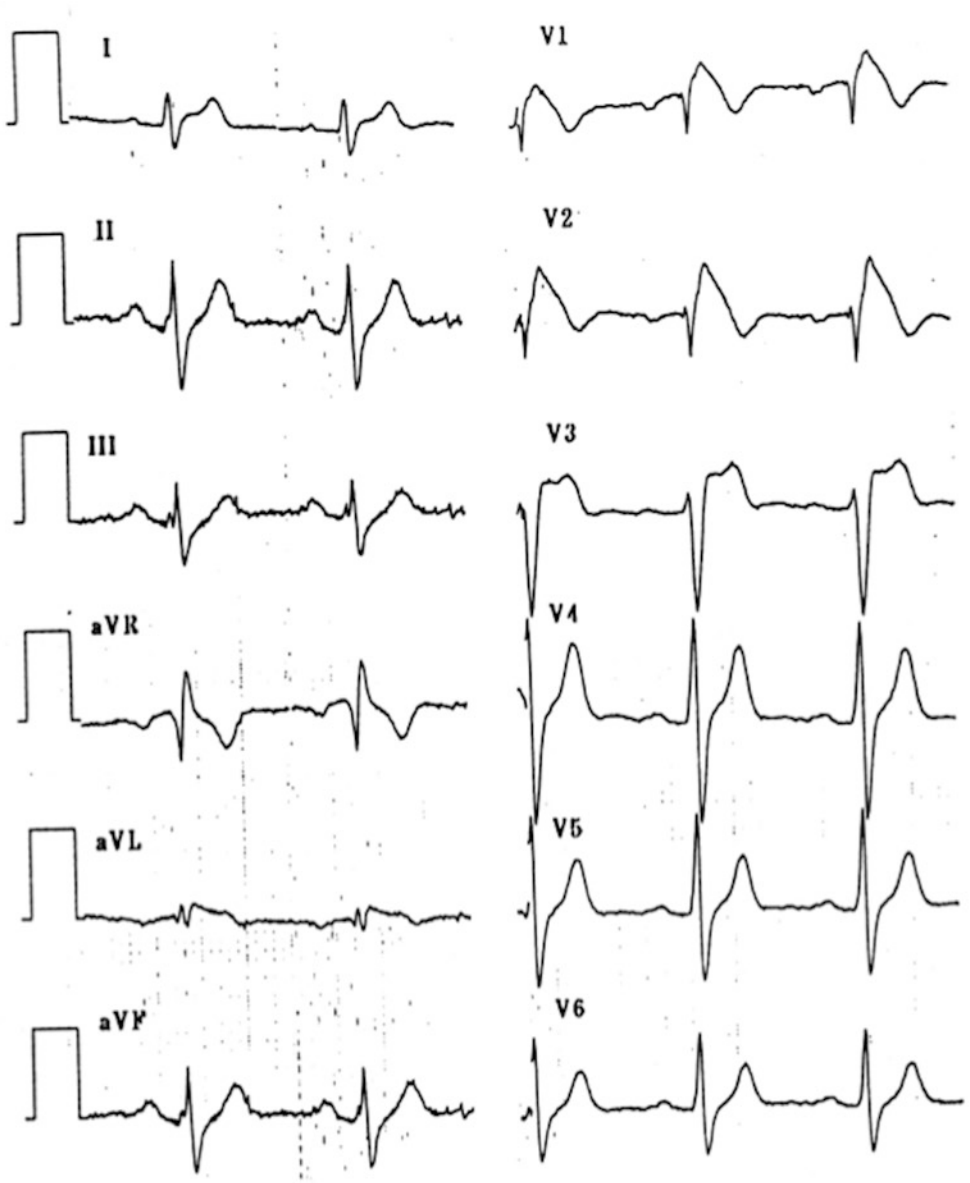

Fig. 17.3 Type 1 Brugada ECG pattern

Electrophysiology testing. The value of the inducibility of VA by programmed electric stimulation (PES) remains controversial. Several consensus documents have addressed this issue and the recommendation of PES for risk stratification has dropped from a IIa indication in the Second Brugada Syndrome Consensus Conference [49] to a IIb in the 2013 Expert Consensus Statement [58]. In a recent study with 403 patients presenting with spontaneous or drug-induced Brugada type I ECG, programmed ventricular stimulation was a good predictor of outcome in individuals with Brugada syndrome. This data suggests that electrophysiology testing might be of special value to guide further management when performed in asymptomatic individuals [59].

Genetic testing. Genetic testing for Brugada syndrome, which typically involves sequencing SCN5A, can be useful in confirming the presence of a mutation in a patient with the suspected diagnosis of Brugada syndrome. In patients with a clinical diagnosis of Brugada syndrome, genetic testing may also allow family screening and risk stratification. However, the genetic and clinical heterogeneity of Brugada syndrome limit the utility of genetic testing, as the absence of a mutation in SCN5A does not exclude Brugada syndrome, and the presence of a mutation in SCN5A does not confirm the diagnosis of Brugada syndrome.

Treatment

Treatment for patients diagnosed with the Brugada syndrome is primarily focused around termination of any ventricular arrhythmias with an implantable cardioverter-defibrillator (ICD). Current guidelines [58] recommend ICD implantation for: patients with Brugada syndrome who have survived SCA or who have documented spontaneous sustained ventricular tachycardia (class I); patients with spontaneous type I Brugada pattern ECG with a history of syncope likely caused by ventricular arrhythmias (class IIa); patients with Brugada syndrome who develop ventricular fibrillation during programmed stimulation during electrophysiology testing (class IIb).

Initial pharmacologic therapy for arrhythmia prevention has been tried in the Brugada syndrome with relatively little success, so ICD implantation should be the first line therapy for nearly all patients. However, patients with the Brugada syndrome who experience recurrent ventricular arrhythmias resulting in ICD shocks may require therapy with an antiarrhythmic drug in an effort to reduce the frequency of ICD shocks.

Isoproterenol has proved to be useful for treating electrical storm in BS. Quinidine has also proved to be useful for treating electrical storm in BS patients [60]. It prevents induction of VF and suppresses spontaneous ventricular arrhythmias, being used in patients with BS and multiple ICD discharges. It has been suggested that it also could be useful as a bridge to ICD, and as an alternative to it in children; however, it has a high rate of secondary effects. Finally, patients with only the Brugada ECG pattern do not require any specific therapy.

The use of RF ablation of the right ventricular epicardium has been initially advocated by Nademannee et al. [61] in patients with electrical storms and has now been extended to patients with a type I ECG and inducible arrhythmias in a very recent series published by Brugada, Pappone et al. [62]. Modifying the right ventricular epicardial layer by using RF ablation universally normalizes the ECG and prevents unmasking it by flecainide and inducibility of arrhythmias in patients with clear abnormal ECG's and inducible arrhythmias before the procedure. Follow-up at 6 months confirms persistence of normal ECG and negative drug challenging with flecainide. How this technique is going to influence the therapy in asymptomatic patients will require larger studies.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic VT (CPVT) is a genetic disorder that generally presents as familial although some sporadic cases have been reported. Basal ECG is normal but adrenergic stimulus like exercise or mental stress can trigger ventricular arrhythmias, ventricular extrasystoles, bidirectional tachycardia (Fig. 17.4) or polymorphic VT and

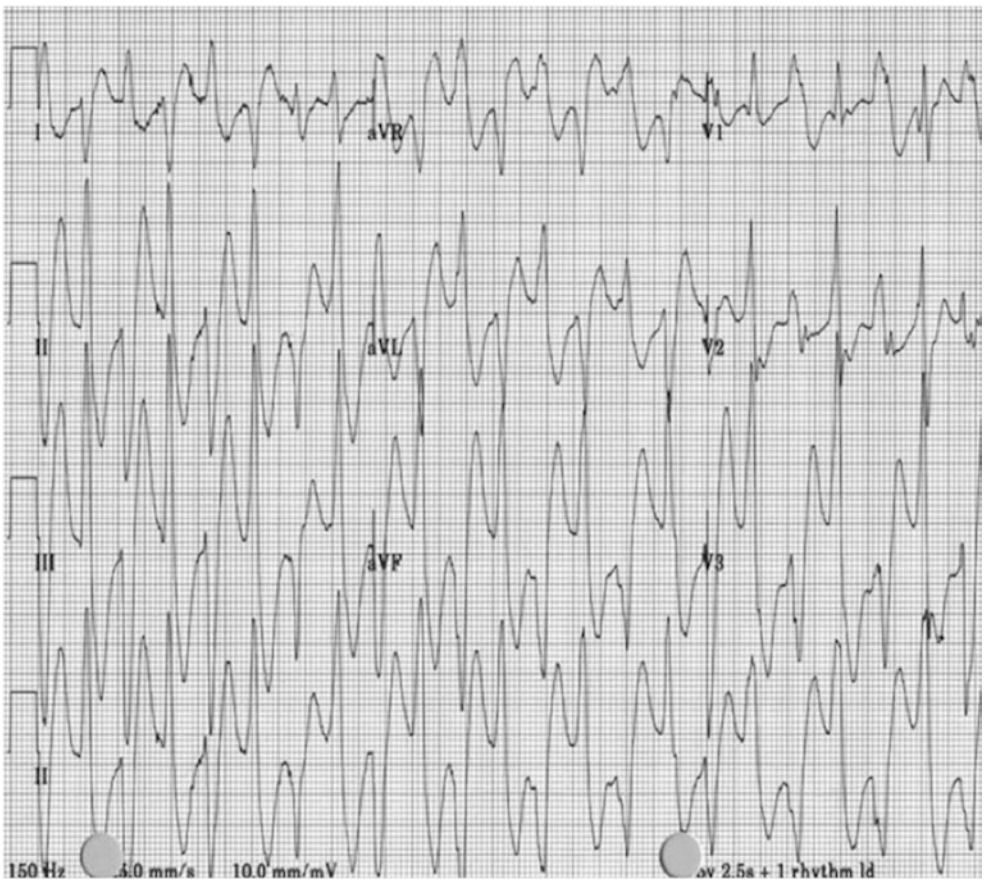

Fig. 17.4 Bidirectional ventricular tachycardia in a patient with diagnosis of CPVT

VF. Risk factors for sudden death include documented VF, a family history of sudden death, and onset of symptoms in childhood. More than 200 genetic abnormalities in different genes have been linked to the disease. The Ryanodine RYR2 gene is the most often altered protein. The mutation produces an excess in the intracellular calcium resulting in late after depolarizations and finally ventricular malignant arrhythmias. Other genes like CASQ2, KCNJ2, CALM1 and TRDN have been also linked to the same phenotypic behaviour. Beta blockers are often given for primary prevention and should be used for secondary prevention, although the response is not uniform. Flecainide has been added in cases with poor response [63]. The role of left cardiac sympathetic denervation in patients refractory to beta blocker therapy has not been clearly defined yet. Patients with risk factors for sudden death and no response to pharmacological therapy often receive an ICD.

Early Repolarization

Early repolarization (ER) is defined as either a sharp well-defined positive deflection or notch immediately following a positive QRS complex at the onset of the ST segment, or the presence of slurring at the terminal part of the QRS complex. Most literature defines ER as being present on the electrocardiogram when there is J-point elevation of ≥0.1 mV in two adjacent leads with either a slurred or notched morphology.

The ER pattern describes the patient with appropriate ECG findings in the absence of symptomatic arrhythmias. The ER syndrome applies to the patient with both appropriate ECG findings and symptomatic arrhythmias.

Persons with either the ER pattern or ER syndrome can have identical findings on surface ECG. However, the mere presence of ER pattern on ECG should not lead to a classification of ER syndrome in the absence of symptoms or documented VF.

The prevalence of ER ranges from 5 to 13%. The perception that ER was a benign finding devoid of clinical significance has changed, with numerous studies suggesting a two- to threefold increased risk of death in those with ER versus those without ER. While ER appears to increase one's risk of sudden cardiac death (SCD), the absolute risk of SCD remains exceedingly low in otherwise healthy people. Therefore the incidental identification of ER should not be interpreted as a high-risk marker for arrhythmic death due to the relatively low odds of SCD based on ER alone.

The purported mechanisms of ER and idiopathic VF all reflect an imbalance in the ion channel currents responsible for the terminal portion of depolarization and the early portion of repolarization.

Given its relatively high prevalence in the general population in comparison to the incidence of idiopathic VF, the ER pattern is almost always an incidental ECG finding. For patients with the incidental finding of the ER pattern on their ECG, observation without therapy is recommended. For patients with ER and ongoing acute VF (VF storm) requiring frequent defibrillation, intravenous isoproterenol is recommended.

For patients with ER syndrome with prior resuscitated SCD due to VF, an ICD should be implanted. In order to prevent recurrent ICD therapies due to VF, quinidine may be useful.

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