

## Ventricular Arrhythmias in Normal Hearts

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Despite advances in the treatment of ventricular tachyarrhythmias, their management continues to challenge clinicians. Ventricular tachyarrhythmias are most commonly seen in patients who have structural heart disease; however, 10% of patients presenting with ventricular tachyarrhythmias have no apparent structural heart disease. These patients are said to have idiopathic ventricular tachycardia (VT) and have been segregated into subtypes defined by QRS morphology, ventricular origin, and response to pharmacologic agents. The management and the prognosis of idiopathic VT differ considerably from VT in the setting of identifiable structural abnormalities.

The diagnosis of idiopathic VT is made after a thorough cardiac evaluation yields normal results. The initial evaluation often consists of the resting ECG and evaluation of ventricular function, both of which are normal between episodes of tachycardia. Further evaluation by signal-averaged ECG also demonstrates normal findings between episodes of tachycardia [1]. An evaluation of coronary perfusion should be considered in appropriate patients to exclude possible coronary artery disease as an etiology of VT. Further studies such as right ventricular (RV) perfusion imaging [2] and RV biopsy [3–5] are rarely performed but may be of use in differentiating between idiopathic VT and VT in the setting of organic heart disease. It is important to note that although the classic definition of idiopathic VT continues to refer to a structurally normal

heart, techniques for assessing myocardial structure and function continue to evolve and provide further insight into possible mechanisms of these arrhythmias. Cardiac MRI may reveal mild structural abnormalities, the significance of which is still debated [6–8]. In addition, positron emission tomography has been used to demonstrate functional autonomic differences in patients who have idiopathic VTs [9,10]. I-131 meta-iodobenzylguanidine imaging staining has inconsistently shown abnormalities in the outflow tract region of some patients manifesting idiopathic VT [11,12]. As the resolution of testing continues to increase to the cellular and molecular level, it is likely that these arrhythmias will be found to have associated abnormalities.

Although subtle abnormalities may be seen on advanced imaging studies in idiopathic VTs, it may be difficult to distinguish normal myocardium from pathologic substrates early in their course. Pathologic conditions such as arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D) demonstrate electrical abnormalities on signal-averaged ECG [13,14], voltage mapping [15], and inducible VT with programmed stimulation. In addition, there are identifiable genetic mutations in desmosomal proteins in some patients who have ARVC/D [16]; however, patients initially diagnosed with idiopathic VT then found to develop ARVC/D have been reported, demonstrating the potential difficulty in differentiating between the two diagnoses [17].

The syndrome of idiopathic VT refers specifically to monomorphic VTs. Polymorphic VTs and ventricular fibrillation have been described in structurally normal hearts but differ from idiopathic VT mechanistically and prognostically.

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Idiopathic VT can be subclassified based on several criteria (eg, mechanism, location, response to pharmacologic therapy). Most commonly, these arrhythmias are subgrouped as outflow tract tachycardias, idiopathic left VTs (ILVTs), and automatic VTs.

### Outflow tract tachycardia

VTs originating from the outflow tracts account for most cases [18]. The outflow tract region typically encompasses the RV region between the pulmonary and tricuspid valves, the basal left ventricle including the outflow tract under the aortic valve, the aortic cusps, and the basal left ventricular (LV) epicardium. The clinical presentation of tachycardias originating from these sites includes isolated monomorphic frequent ventricular premature complexes (VPCs), repetitive nonsustained runs of VT, and less commonly sustained VT [19,20]. Paroxysmal sustained VT is typically precipitated by exercise or emotional stress. Repetitive nonsustained VT is also seen with exercise testing and usually occurs during recovery, often with a reproducible relationship to heart rate. In female patients, there is also a strong association of the occurrence of tachycardia related to the menstrual cycle [21].

Based on seminal studies by Lerman and colleagues [22,23] delayed afterdepolarization (DAD)-mediated triggered activity is believed to be the mechanism underlying these arrhythmias. DAD-triggered activity is typically mediated by intracellular calcium overload. As a result, outflow tract tachycardias are frequently precipitated by catecholaminergic stimulation, resulting in an increase in intracellular cAMP and calcium. Thus, these rhythms are usually induced by rapid stimulation with or without isoproterenol infusion. Furthermore, this dependence on cAMP explains their sensitivity to  $\beta$ -blockade, calcium channel blockade, and adenosine.

Although the outflow tract occupies a relatively narrow anatomic zone, the ECG manifestations of tachycardias originating from this region can have a wide range. Nevertheless, the ECG morphologies of these arrhythmias are often predictable, making this an important tool in accurately localizing their site of origin even before the patient is brought to the electrophysiology laboratory. Determining this site is important for procedural planning and for discussion of specific risks with the patient.

RV outflow tract (RVOT) tachycardias are the most common form of outflow tract VTs, accounting for approximately 75% of cases. RVOT VTs have a characteristic left bundle branch block (LBBB) pattern with an inferior axis and a QRS transition (ie, from negative to positive) in the precordial lead  $V_3$  or  $V_4$  (Fig. 1). Several studies have demonstrated that the 12-lead ECG can be used to further localize the site of origin of these tachycardias. Jadonath and colleagues [24] divided the RVOT region into nine regions and used QRS morphology in leads I and aVL in addition to R wave transition to differentiate anterior from posterior RVOT sites. Anterior sites demonstrated a Q wave (Q or qR) in lead I and a QS in lead aVL. Posterior sites demonstrated an R wave in lead I and an early precordial transition ( $R > S$  in  $V_3$ ). In all patients, a QS was noted in aVR, and monophasic R waves were seen in the inferior leads. Further refinement in these observations was made by Dixit and colleagues [25] to more accurately differentiate septal from free wall RVOT VTs. Typically, RVOT VTs originating from septal locations manifests taller, narrower monophasic R waves in the inferior leads compared with the corresponding free wall locations. Furthermore, free wall RVOT VTs demonstrate notching in the inferior leads and a later transition in the precordial leads ( $>V_3$ ) compared with septal RVOT VTs. Further localization of VT originating in the superior RVOT can be aided by the QRS morphology in lead I. RVOT VTs originating from posterior locations manifest predominantly positive QRS complexes in lead I, and anterior sites manifest predominantly negative complexes. RVOT VTs originating between the anterior and posterior locations typically demonstrate a multiphasic QRS morphology in this lead (Fig. 2).

LVOT tachycardias manifest clinical features similar to RVOT VTs, probably because they share the same underlying mechanism [26,27]. The ECG has again been shown to help differentiate RVOT tachycardias from LVOT tachycardias. VT arising from the LVOT has been shown to manifest two patterns on ECG: (1) a right bundle inferior axis with a dominant R wave in  $V_1$  and lack of precordial transition with or without a late appearing S wave in  $V_6$  and  $V_2$ ; and (2) a left bundle inferior axis morphology with an early precordial R wave transition ( $\geq V_2$ ) [28,29]. Further localization of VT originating from this region can be aided by the QRS morphology in lead I, R wave morphology in lead



Fig. 1. Twelve-lead ECG of VT originating from the RVOT. Note the LBBB morphology with the late transition (ie, the QRS complex is not positive until lead  $V_4$ ) in the precordial leads and an inferior axis in the limb leads.

$V_1$ , and the ratio of R waves in limb leads II and III [18].

Tachycardia manifesting clinical features similar to RVOT and LVOT has also been demonstrated from the aortic cusp region (Fig. 3). Depending on the site of origin from the right or left coronary cusp, these tachycardias produce right bundle branch block (RBBB) or LBBB morphology. In the authors' experience, the QRS morphology in leads I and  $V_1$  can help differentiate VT originating from the cusps and the aortomitral continuity. VT originating from the left coronary cusp or the aortomitral continuity often demonstrates a terminal S wave in lead I [30]. Furthermore, Ouyang and colleagues [31] described quantitative ECG measurements to discriminate RVOT tachycardia from aortic cusp tachycardia. In their study, R wave duration and the R/S wave amplitude ratio in leads  $V_1$  and  $V_2$  were greater in tachycardias originating from the cusp compared with the RVOT. In addition, precordial lead transition was earlier in cusp VT, occurring before lead  $V_3$  (Fig. 4). Other investigators have also reported features that may help with this differentiation, such as the absence of an S wave in  $V_5$  or  $V_6$ , which has demonstrated a specificity of 88% for cusp VT compared with RVOT VT [32]. Although VT can arise from the right

coronary cusp or noncoronary cusp, most VTs seem to arise from the left cusp and specifically from the junction of the left and right cusps. Given the proximity of the right coronary cusp to the RVOT, it is not surprising that ECG-based differentiating algorithms may not be consistently accurate. Ultimately, localization must be based on the earliest intracardiac activation or on pace mapping (Fig. 5).

Infrequently (9%–13% of idiopathic VT), outflow tract VT can originate from epicardial locations [33,34]. Often, the focus arises from the proximal coronary venous vasculature [33]. The ECGm may be useful in suggesting an epicardial origin (Fig. 6). Tada and colleagues [34] found that R wave amplitude was significantly greater in the inferior leads, that lead I had an S wave as part of an rS or QS pattern, and that Q wave amplitude was greater in aVL compared with aVR (ratio  $>1.4$ ) in the epicardial group compared with an RV endocardial or an LV endocardial group. In addition, the LV epicardial group had a distinct R wave in  $V_1$  with a greater amplitude than in the RV endocardial group and significant S waves in  $V_1$  ( $>1.2$  mV) and  $V_2$ . The authors' data demonstrate that a Q wave in lead I more commonly identifies VT from an epicardial site compared with an endocardial site; however,



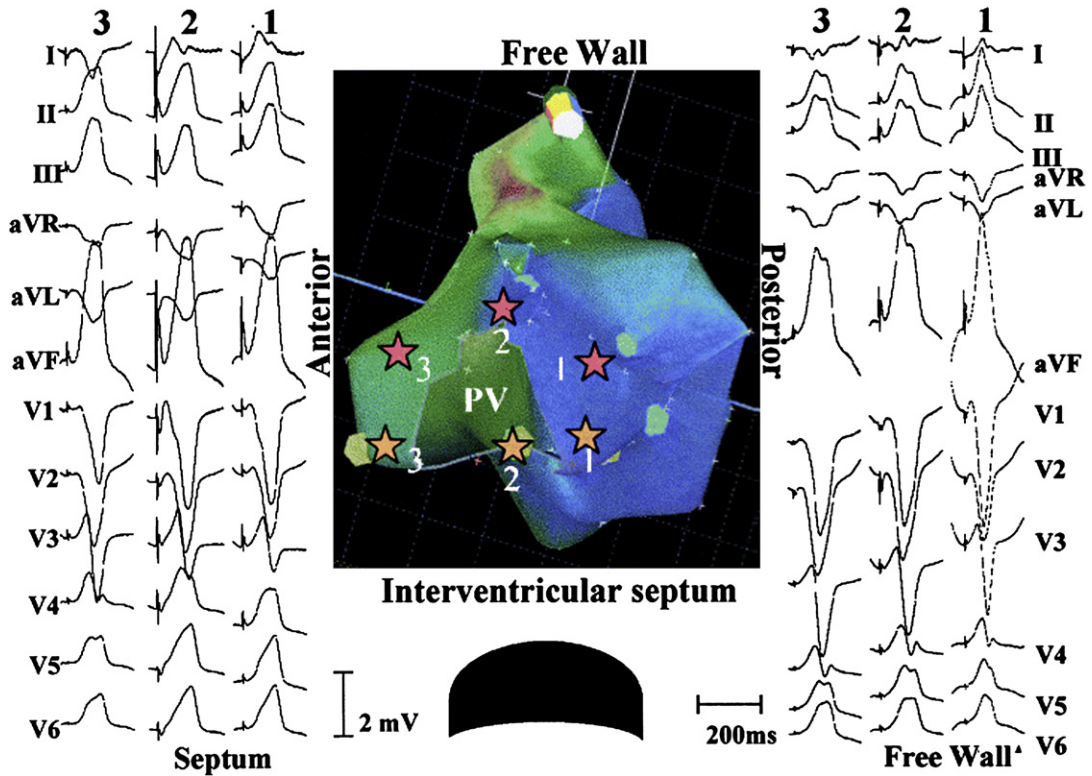


Fig. 2. Twelve-lead ECG pace maps from anterior, intermediate, and posterior sites (3, 2, and 1, respectively) of the RVOT septum and free wall. All pace maps show an LBBB morphology and inferior frontal plane axis. Lead I is negative in the anterior sites (site 3) and positive in the posterior sites (site 1). R waves in the inferior leads are broader, shorter, and notched in free wall pace map sites. (From Dixit S, Gerstenfeld EP, Lin D, et al. Electrocardiographic patterns of superior right ventricular outflow tract tachycardias: distinguishing septal and free wall sites of origin. *J Cardiovasc Electrophysiol* 2003. p. 3; with permission.)

other morphologic criteria are site specific, reflecting local ventricular activation. Furthermore, ECG features distinguishing epicardial VT arising from the left ventricle do not reliably diagnose epicardial VT from the right ventricle [35,36]. In an attempt to increase the reliability of ECG criteria in diagnosing epicardial VT, Daniels and colleagues [33] demonstrated that a precordial maximum deflection index greater than 0.55 reliably localized VT to the epicardium with a sensitivity of 100% and a specificity of 98%.

Thus, if carefully analyzed, the 12-lead ECG remains a powerful tool in localizing the site of origin of outflow tract tachycardias and can greatly facilitate accurate localization and successful ablation of these arrhythmias.

Outflow tract VT has good prognosis with a benign course in most patients [19,20,37,38]; however, patients identified with RVOT VPCs have developed spontaneous ventricular

fibrillation or polymorphic VT. Typically, polymorphic VT is caused by unusually short-coupled RVOT VPCs; these patients appear to respond well to successful VPC ablation [38–40]. In addition, frequent VPCs may cause a tachycardia-mediated cardiomyopathy with LV dysfunction; LV function may recover following VPC ablation [41,42]. Finally, it is important to differentiate outflow tract VT from ARVC/D because ARVC/D is associated with a significantly worse prognosis, including sudden cardiac death [17,43,44].

Management of outflow tract VTs may encompass medical therapy or catheter ablation. The initial decision to treat is dictated by frequency and severity of symptoms. Attention to the coupling interval of extrasystoles may offer clues to a potentially more malignant prognosis and may suggest catheter ablation as the initial choice of therapy [45]. Because triggered activity is

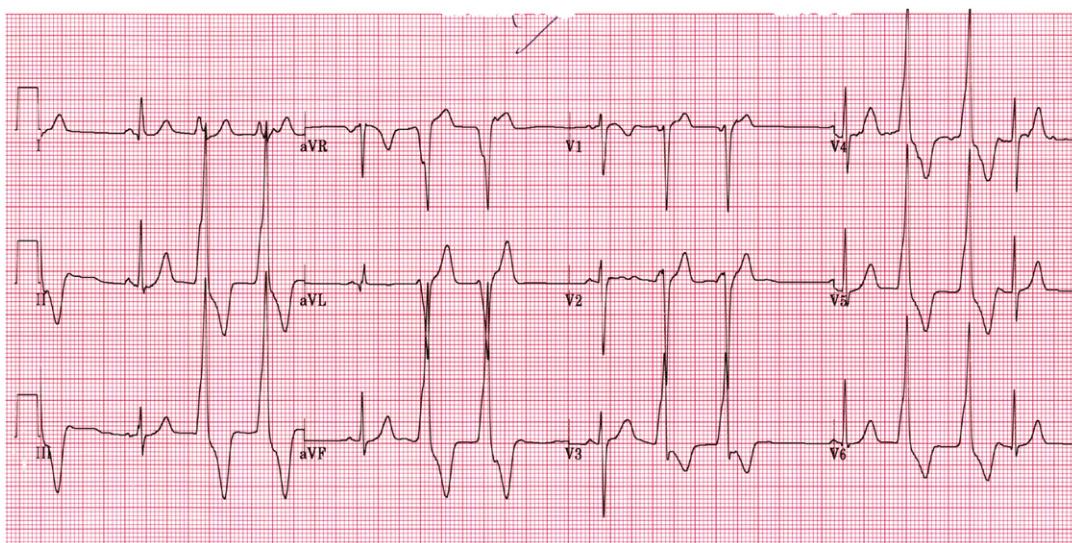


Fig. 3. Twelve-lead ECG of premature ventricular contraction originating from the coronary cusp. An LBBB morphology with transition by  $V_3$ , tall R waves in the inferior leads, and an s wave in lead I suggest the VPC arises from the left coronary cusp.

the cause of most outflow tract tachycardias, adenosine, verapamil,  $\beta$ -blockers, and carotid sinus massage often terminate the tachycardia acutely.  $\beta$ -blockers and calcium channel blockers may be used for chronic suppressive therapy; the efficacy in clinical studies has been variable, with success rates of up to 67% in patients who have typical RVOT tachycardia [46]. In some patients who have breakthrough tachycardia on  $\beta$ -blocker or calcium channel blockers, class I antiarrhythmic or class III antiarrhythmic therapy has been shown to be effective [1,47].

Although medical therapy may be effective in patients who have mild to moderate symptoms, it is frequently ineffective in patients who have severe symptoms [48]. Catheter ablation using radiofrequency energy has evolved significantly and currently has a high success rate (>80%) in treating these arrhythmias [49–54]. In planning ablation, the 12-lead ECG is used to localize the site of origin of tachycardia. Tachycardia localization involves intracardiac activation and pace mapping. Pace mapping is useful because typically the site of origin is focal and, because the underlying tissue is normal, pacing is performed with a low output, resulting in a small discrete area of depolarization. Thus, when pace mapping is performed at the site of origin of the clinical arrhythmia, the ECG should mimic the clinical arrhythmia perfectly (12/12, including notches)

[53]. Activation mapping is another approach. Because these arrhythmias are mediated by triggered activity, the electrogram at the site of origin typically precedes the onset of the QRS by approximately 20 milliseconds. An exception to this may be in cusp VT, in which impressive prepotentials (~50 milliseconds) may be seen during VPCs that correspond to late potentials during sinus rhythm [31]. Electroanatomic re-creation of the three-dimensional anatomy can be very helpful for catheter mapping and can facilitate accurate localization of the site of origin. If incessant, the three-dimensional anatomy should ideally be created during the tachycardia, which should be able to localize the earliest site to a small region (<5 mm) with centrifugal activation; typically, pace mapping from this region should achieve a perfect match. Rarely, there may be lack of congruence between the activation and pace map localization because the latter can occasionally be satisfactory over a large area. Predictors for successful ablation include a single VT morphology, accurate pace maps, the absence of a deltalike wave at the beginning of the QRS during tachycardia, and the ability to use pace mapping and activation mapping [54,55]. Although ablation of outflow tract tachycardias may be performed successfully in many cases, some tachycardias arise from the epicardium, necessitating ablation from the great cardiac vein [56] or the epicardium itself

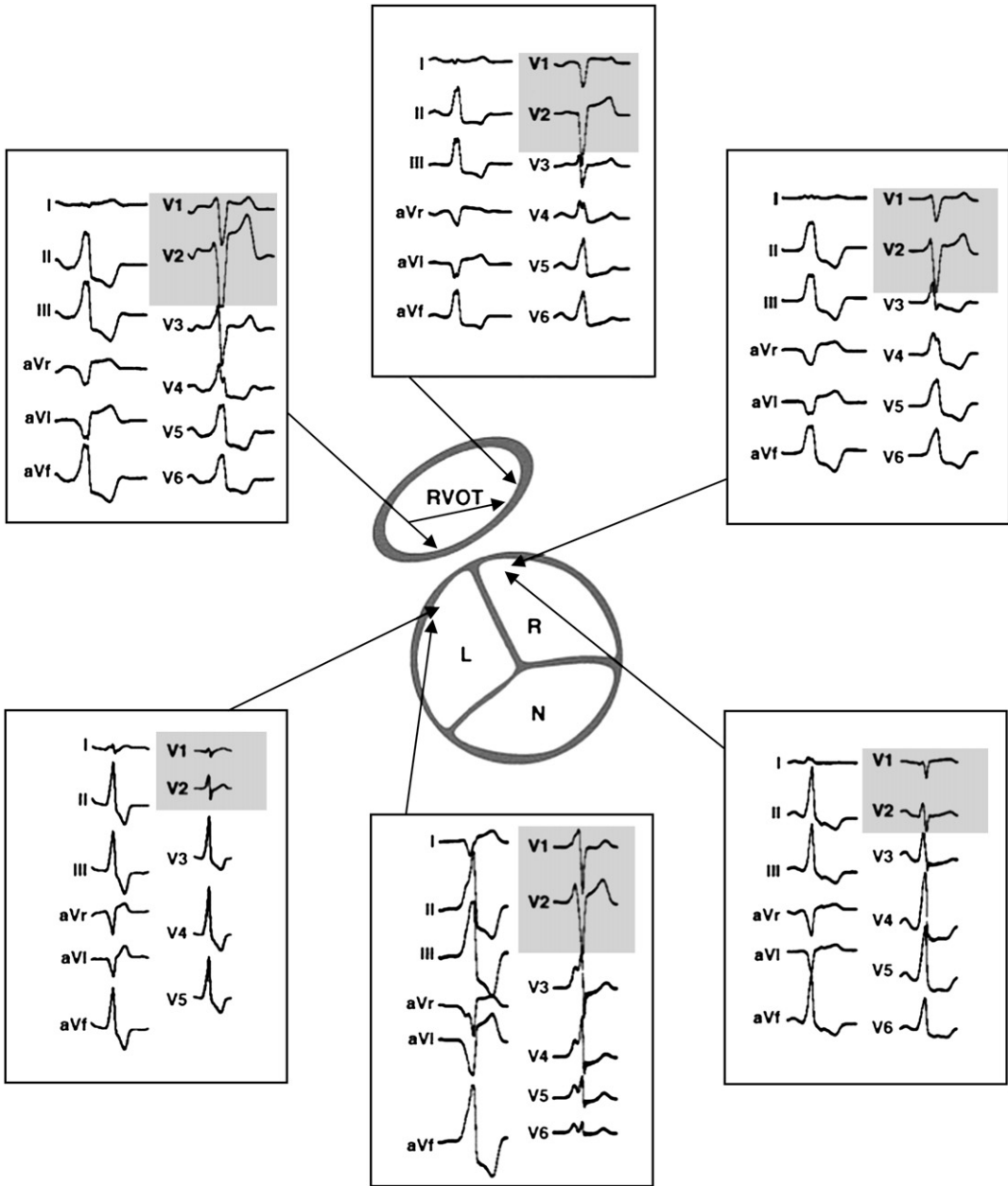


Fig. 4. Twelve-lead ECG of characteristic morphologies of VT originating from the RVOT, the left coronary cusp (L), and the right coronary cusp (R). N, noncoronary cusp. (From Ouyang F, Fotuhi P, Ho SY, et al. Repetitive monomorphic ventricular tachycardia originating from the aortic sinus cusp: electrocardiographic characterization for guiding catheter ablation. *J Am Coll Cardiol* 2002;39(3):503; with permission.)

using a pericardial puncture technique [57]. Coronary angiography is performed before ablation on the epicardium or in the aortic sinus because damage to the coronary arteries may occur [58]. Complications during outflow tract VT ablation are

rare but can include development of RBBB (1%) and cardiac perforation, which may or may not result in tamponade. There are rare case reports of damage to the coronary artery (left anterior descending) during ablation in the cusp region [59].

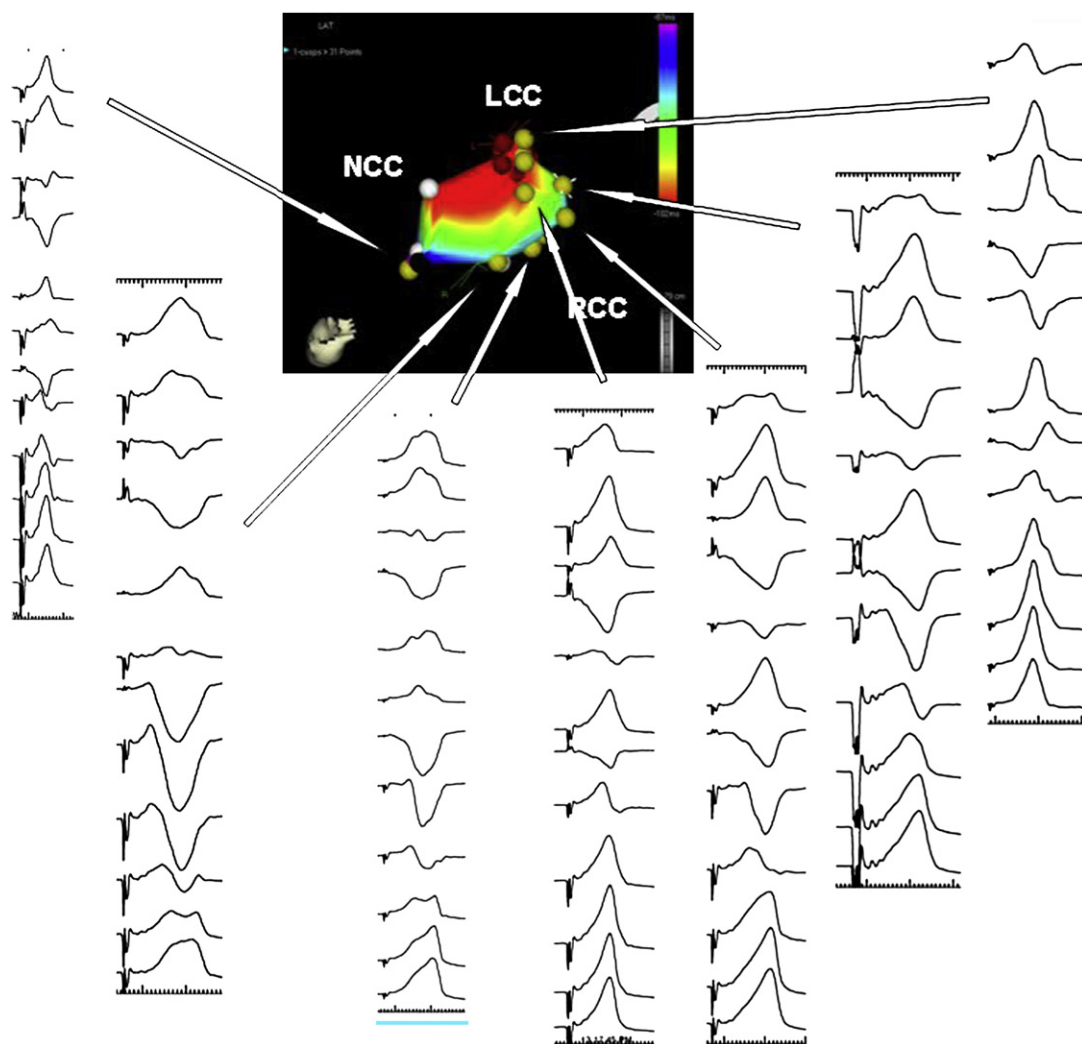


Fig. 5. Pace map morphologies of VT originating from the left coronary cusp (LCC), right coronary cusp (RCC), and noncoronary cusp (NCC).

Long-term cure rates after a successful initial ablation are high, and the overall recurrence rate is approximately 10% [54,60,61].

### Idiopathic left ventricular tachycardia

VTs in the normal heart may also arise from the left ventricle. The most common form of ILVT is verapamil-sensitive tachycardia (Fig. 7). First described by Zipes and colleagues [62] in 1979, the tachycardia had the following triad: (1) induction with atrial pacing, (2) RBBB morphology with left axis deviation, and (3) occurrence in patients who did not have structural

heart disease. Belhassen and colleagues [63] demonstrated verapamil sensitivity of the tachycardia.

ILVT is seen most often in patients between 15 and 40 years old. Typical symptoms include palpitations, fatigue, and presyncope. Syncope and sudden cardiac death are rare but have been described [64]. Incessant tachycardia leading to a tachycardia-induced cardiomyopathy has also been described but is unusual because episodes are typically infrequent [65]. Most episodes occur at rest, making exercise testing unreliable in assessing the tachycardia.

The anatomic basis for ILVT is unclear. By endocardial activation mapping during tachycardia,



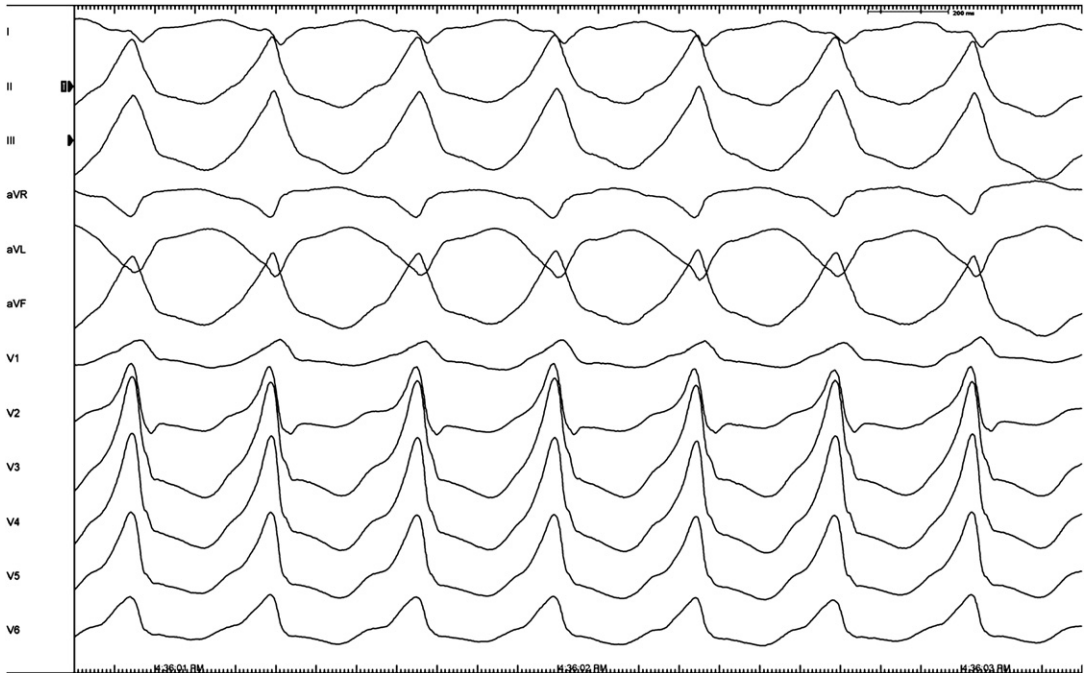


Fig. 6. Twelve-lead ECG of VT originating from the epicardium. There is a Q wave in lead I and a terminal S wave in V<sub>2</sub> (Paper speed 100 mm/s).

the earliest site of activation is in the region of the inferoposterior LV septum. Nakagawa and colleagues [66] recorded high-frequency potentials preceding the earliest ventricular activation in sinus rhythm and during tachycardia thought to represent activation of a component of the left

posterior fascicle. Late diastolic potentials (LDPs) have been identified more recently that precede the Purkinje potentials seen by Nakagawa and colleagues [66] and appear to be located nearer the main portion of the left bundle branch (Fig. 8) [67]. Some data, however, suggest that the

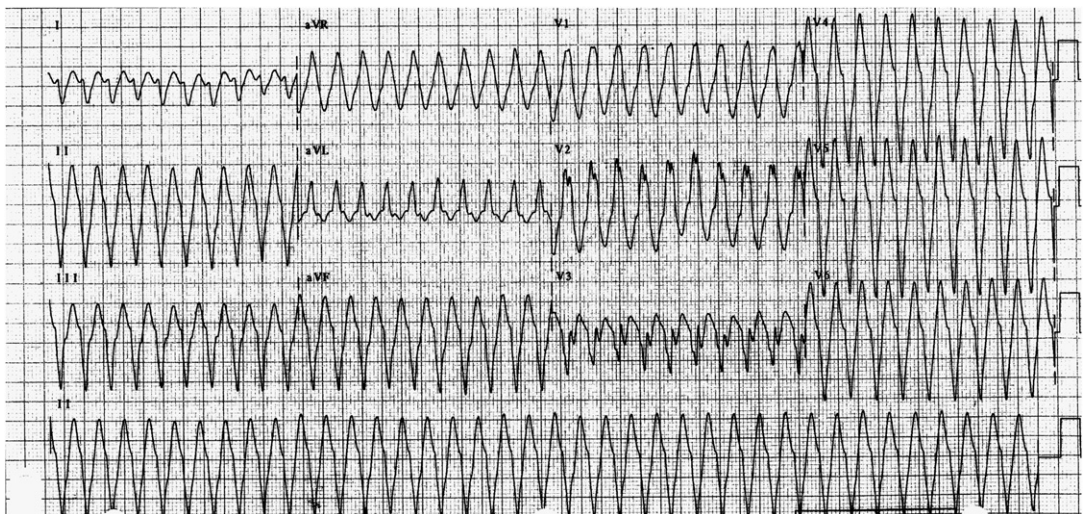


Fig. 7. Twelve-lead ECG of VT with an RBBB, a right superior axis in the frontal plane, and a late precordial transition consistent with origination from the left posterior fascicle.



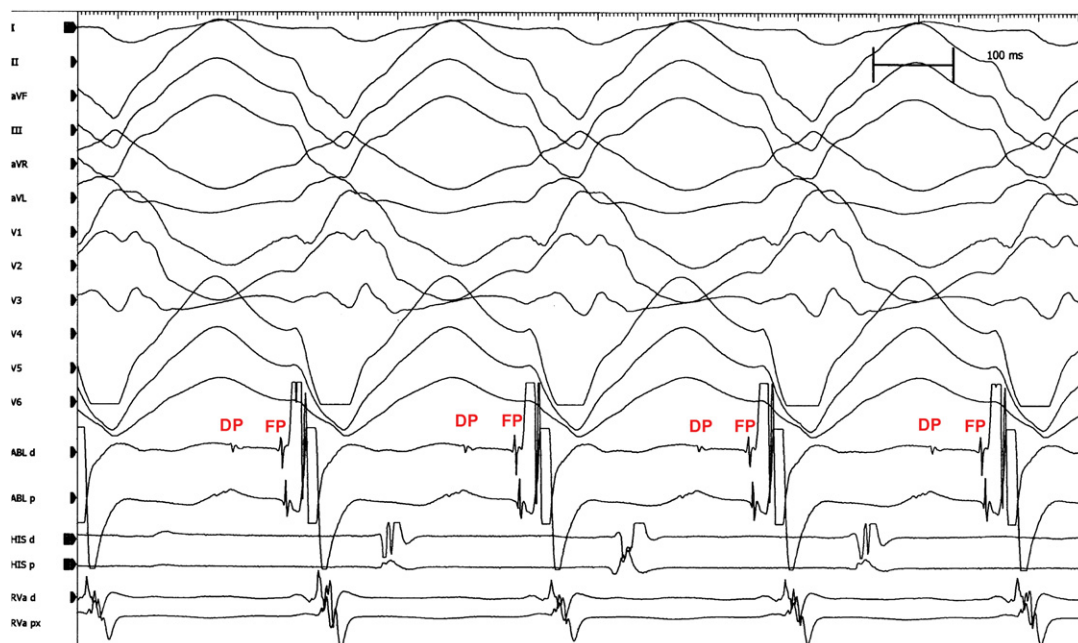


Fig. 8. Twelve-lead ECG of VT. The ablation catheter is in the region of the left posterior fascicle. Intracardiac electrograms demonstrate a mid-diastolic potential (DP) and a fascicular potential (FP) (Courtesy of H. Hsia, MD, Stanford, CA).

tachycardia originates from a false tendon that extends from the posteroinferior left ventricle to the basal septum, with resection of the tendon or ablation at the septal insertion site eliminating tachycardia [68–70]. Furthermore, one study found a false tendon on transthoracic echocardiography extending from the posteroinferior LV free wall to the septum in 15 of 15 patients who had ILVT, whereas only 5% of control subjects were found to have a false tendon. The exact role the tendon plays in the tachycardia remains unclear because the specificity may be low; another study confirmed the presence of a false tendon in 17 of 18 patients who had fascicular VT but also identified false tendons in 35 of 40 control subjects [71].

Most evidence indicates localized reentry as the predominant mechanism in verapamil-sensitive ILVT. Tachycardia can be initiated and terminated with programmed atrial or ventricular stimulation, it demonstrates an inverse relationship between the coupling interval of the initiating extrastimulus and the initial tachycardia QRS, and it can be entrained [63,64,72,73]. Okumura and colleagues [74] further characterized the nature of the tachycardia circuit. They demonstrated entrainment with a zone of slow conduction between the RVOT (pacing site) and the earliest

site of activation in the LV (compared with the RV apex). Tsuchiya and colleagues [67] further localized the zone of slow conduction to the interval between the LDP and the Purkinje potential. Furthermore, variations in VT cycle length are preceded by variations in the LDP–Purkinje potential interval. In addition, the zone of slow conduction is dependent partly on calcium channel-dependent conduction and partly on depressed sodium channel-dependent conduction because intravenous verapamil and lidocaine lead to prolongation of the tachycardia cycle length that was entirely due to prolongation in the zone of slow conduction. The entrance site to the zone of slow conduction is thought to be near the base of the left interventricular septum, near the site of the LDP. Taken together, the data suggest a reentrant circuit with an entrance near the LDP, a zone of slow conduction between the LDP and the Purkinje potential, and an exit site distal to the Purkinje potential.

Because ILVT affects patients who have structurally normal hearts, the baseline 12-lead ECG is normal in most patients. Corresponding to its LV origin, ILVT has a right bundle, left superior frontal plane axis morphology with a relatively narrow QRS duration (typically no longer than

140 milliseconds), and an RS interval less than 80 milliseconds [75] in most patients, suggesting an exit site near the area of the left posterior fascicle. A small proportion of patients have VT with a right bundle, right frontal plane axis morphology, suggesting an exit near the area of the left anterior fascicle [76]. Because of the relatively narrow, complex QRS and the response to verapamil, ILVT may be confused with supraventricular tachycardia with aberrancy.

As with outflow tract VTs, the long-term prognosis of patients who have ILVT is very good [48,77]. Patients who have incessant tachycardia, however, may develop a tachycardia-related cardiomyopathy [65]. Intravenous verapamil is effective in acutely terminating VT [48,72]. Patients who have mild to moderate symptoms may be treated chronically with verapamil, but this medical therapy is often ineffective in patients who have severe symptoms [48].

Patients who have ILVT associated with significant symptoms or who are intolerant or resistant to medical therapy should be considered for radiofrequency ablation. Numerous strategies have been employed to identify the ideal site for ablation, including pace mapping, endocardial activation mapping [78–80], identifying Purkinje potentials [66], and identifying late diastolic

potentials [67]. Initial attempts using endocardial activation and pace mapping characterized successful ablation sites as areas of activation 30 milliseconds earlier than the onset of the QRS during tachycardia and with a pace map similar to tachycardia. Of note, there is not a consistent correlation between mapping based on pace mapping (which identifies the circuit exit) and activation mapping (which identifies more proximal portions of the circuit) because the circuit in ILVT has a significant size. Others have described successful ablation sites as being marked by areas of high-frequency Purkinje potentials that precede the earliest ventricular activation during tachycardia and may be located away from the site of earliest ventricular activation. Ablation at such an area terminates VT and prevents re-induction; however, these potentials are not always seen during VT [54]. More recent data have suggested that ablation of the reentrant circuit at the site of the late diastolic potential also terminates VT successfully without recurrence [67,78]. These studies depend on the induction of tachycardia, which may be difficult in the electrophysiology laboratory in some patients. Ouyang and colleagues [81] demonstrated an abnormal potential signifying a retrograde Purkinje potential identified during sinus rhythm in patients who had ILVT. In three

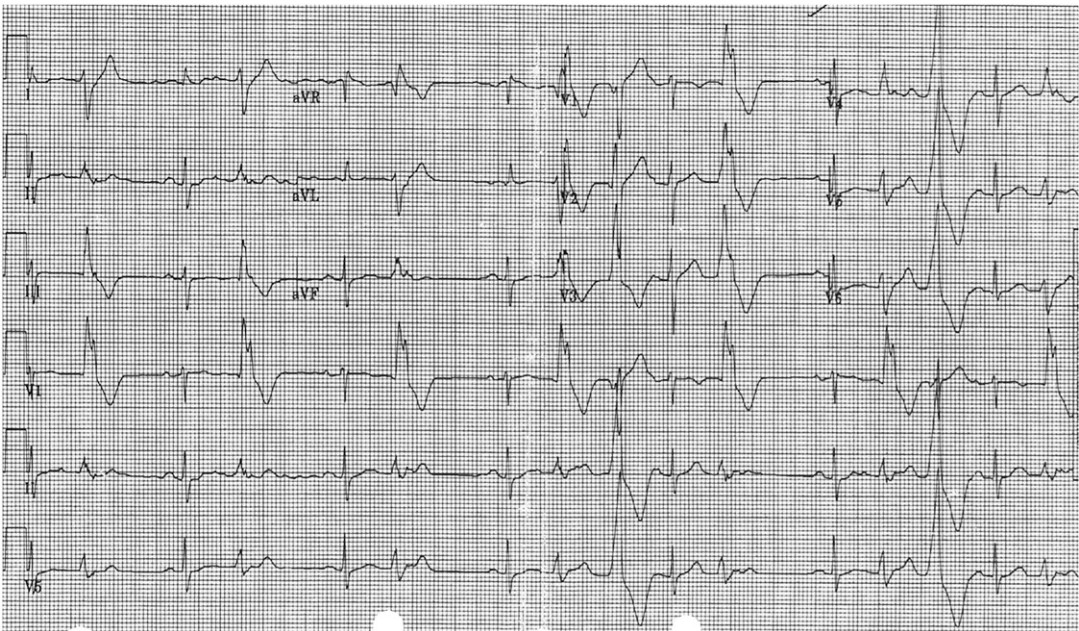


Fig. 9. Twelve-lead ECG of VPCs arising from the coronary cusp and from the anterior papillary muscle consistent with automatic VPCs.

patients, ablation was performed during sinus rhythm at the site of the retrograde Purkinje potential, resulting in freedom from symptoms on no antiarrhythmic therapy during a mean follow-up of 9 months. More recently, Lin and colleagues [82] demonstrated that an empiric linear lesion placed in the area of posterior fascicle and guided by Purkinje potentials was successful in patients who could not be tachycardia induced during the procedure. Long-term success after catheter ablation is more than 90%, with rare complications.

### Automatic ventricular tachycardia

Also referred to as adrenergic or propranolol-sensitive VT, automatic VT is usually seen in patients younger than 50 years and is often precipitated by exercise. Automatic VT can arise from anywhere within the right or left heart, although there are several areas that appear to be more common, such as around the mitral annulus, the papillary muscles, the para-Hisian area, and the RV inflow tract (Fig. 9). Thus, the ECG may demonstrate an RBBB or LBBB morphology and may present as monomorphic or polymorphic VT. It is important to recognize that VT with these "atypical" (ie, nonoutflow tract) signatures does not necessarily imply the presence of structural heart disease, particularly ARVC/D. It is thought to result from adrenergically mediated automaticity because it is induced with exercise and catecholamines, is sensitive to  $\beta$ -blockers, is unresponsive to calcium channel blockers, and cannot be initiated with programmed stimulation [83]. Although the underlying mechanism of this arrhythmia has not been studied extensively, it is thought that some forms of this entity may be caused by automaticity from within the Purkinje fibers mediated by  $I_f$  [84]. Reports of incessant VT have been reported to cause cardiomyopathy, with one report of VT in a patient who had pheochromocytoma resolving with resection of the tumor [85].

### Summary

VT in the structurally normal heart accounts for approximately 10% of cases. Although the overall prognosis is relatively good, with a benign course in most patients, these arrhythmias can lead to significant symptoms. Our understanding of these arrhythmias has progressed significantly,

leading to effective therapies targeting their underlying mechanism. In many cases, catheter ablation is successful and the therapy of choice in patients who have sufficient symptoms.

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