Arrhythmias originating from the right ventricular outflow tract: How to distinguish “malignant” from “benign”?

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Idiopathic ventricular tachycardia (VT) originating from the right ventricular outflow tract (RVOT) in patients without structural heart diseases is generally considered as a benign ventricular arrhythmia (VA). However, “malignant” VA, ventricular fibrillation (VF), and/or polymorphic VT are occasionally initiated by VT or ventricular premature contraction (VPC) originating from the RVOT. In this review article, previous reports describing the malignant form of idiopathic RVOT VT are reviewed, and it is discussed how to distinguish the malignant form from the “benign” form of idiopathic VT originating from the RVOT.

KEYWORDS Ventricular fibrillation; Polymorphic ventricular tachycardia; Sudden death; Catheter ablation

Introduction

Ventricular tachycardia (VT) and ventricular premature contraction (VPC) originating from the right ventricular outflow tract (RVOT) are often observed in patients without structural heart diseases and are generally considered as benign ventricular arrhythmias (VAs).1,2 It is important to distinguish an idiopathic RVOT VT from a VT caused by structural heart diseases, such as arrhythmogenic right ventricular dysplasia (ARVD), in which the RVOT is one of the origins of malignant VT.3 The diagnosis of ARVD can be accomplished by demonstrating morphological abnormalities of the right ventricle with cardiac imaging, that is, echocardiography, magnetic resonance imaging (MRI)4 or computed tomography, and so on. However, it is not always easy to detect subtle right ventricular (RV) morphological abnormalities at an early stage with cardiac imaging.4 Idiopathic VT originating from the RVOT shows a left bundle-branch block configuration in the precordial leads and an inferior axis (normal axis or right axial deviation) in the limb leads (Figure 1A). Radiofrequency catheter ablation has become a primary therapy for idiopathic VT originating from the RVOT2; the success rates are approximately 90%, and the recurrence rates are generally low.5–7 Approximate localization of the VT origin can be estimated by the QRS configuration during VT or VPC. Septal origin in the RVOT is suggested by QRS duration <140 ms, whereas free-wall origin is suggested by QRS duration ≥140 ms associated with notches in the downslope of QRS in inferior leads (II, III, aVF).8,9 Deeper S waves in aVR lead than in aVL lead indicate rightward inferior origin, while deeper S waves in aVL than in aVR indicate leftward superior origin. Precise localization of the VT origin in the RVOT for radiofrequency catheter ablation is determined by the combined use of pace mapping during sinus rhythm and activation mapping during VT or VPC in electrophysiological study.

Idiopathic VT originating from the RVOT usually shows a monomorphic pattern of VT (Figure 1A), with nonsustained VT separated by several sinus beats and frequent VPCs. Idiopathic VT is generally catecholamine sensitive and is often induced with exercise or infusion of catecholamine, such as isoproterenol and epinephrine. The mechanism of idiopathic RVOT VT is thought to be triggered activity due to cAMP-mediated delayed afterdepolarizations; therefore, adenosine or adenosine triphosphate is effective in terminating RVOT VT.5,10 β-Blockers are generally believed to be effective in preventing the recurrence of RVOT VT.

Although idiopathic VT originating from RVOT is generally considered benign (Figure 1A), more malignant ventricular arrhythmias, ventricular fibrillation (VF), and/or polymorphic VT are occasionally initiated by VT or VPC originating from RVOT11–14 (Figure 1B, 1C). In this contemporary review, previous reports demonstrating the malignant form of idiopathic VT originating from the RVOT are reviewed, and it is discussed how to distinguish the malignant form from the benign form of idiopathic VT originating from RVOT.
Malignant form of idiopathic VT originating from RVOT: Previous reports

Since the late 1980s, idiopathic VF or polymorphic VT has been systematically reported in patients without organic heart disease or any identifiable etiology.\textsuperscript{15,16} It is reported that such malignant VF or polymorphic VT is commonly initiated by a VPC with a very short coupling interval (CI). The morphologies of the initiating VPCs have been reported several times, and most showed a left bundle branch block (LBBB) pattern with a superior axis,\textsuperscript{16} suggesting that the origin of the VPCs, which initiate VF or polymorphic VT, were the RV apex or RV inferior wall. In 1994, Leenhardt and coworkers\textsuperscript{16} reported 14 patients with a new electrocardiographic (ECG) entity of a short-coupled variant of torsades de pointes, among whom the configuration of most of the initiating VPC was an LBBB pattern with a superior axis. In only one patient, the configuration of the initiating VPC was a LBBB pattern with a right axial deviation; however, the origin of the initiating VPC was not clearly suggested to be in the RVOT. To the best of our knowledge, Haissaguerre et al\textsuperscript{11} were the first to demonstrate that the origin of VPCs initiating idiopathic VF was the RVOT in a minority of patients from their series. They recruited 27 patients who were resuscitated from recurrent episodes of primary idiopathic VF. The first initiating VPCs were observed during the electrophysiologic study and could be mapped in all 27 patients. The origin of the VPCs was mapped in the RVOT in four of 27 patients, and the VPCs were successfully eliminated by radiofrequency catheter ablation. Viskin and coworkers\textsuperscript{12} described three patients who originally presented with typical benign-looking VT originating from RVOT but who developed malignant polymorphic VT during follow-up. Noda and coworkers\textsuperscript{13} enrolled 16 patients who showed spontaneous VF (n = 5) or polymorphic VT (n = 11) initiated by VPC originating from RVOT among 101 consecutive patients.

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\caption{A: Twelve-lead ECG of benign form of idiopathic monomorphic VT originating from RVOT showing left bundle branch morphology with normal axis. B: Twelve-lead ECG of malignant form of idiopathic polymorphic VT originating from RVOT. Note that the initiating VPC showed left bundle branch morphology with inferior axis (asterisks). C: Initiation of VF recorded by a monitoring ECG in a patient with the malignant form of idiopathic VT originating from RVOT. Note that the QRS morphology of the initiating VPC was identical to that of the preceding isolated VPC (asterisks). Modified from reference 13 with permission.}
\end{figure}
in whom radiofrequency catheter ablation was conducted for treatment of VT or VPCs arising from RVOT. Our data indicated that the malignant form of idiopathic VT was present in 16% of the patients with idiopathic VT originating from RVOT; however, this high percentage represents a referral bias, since patients with the malignant form of idiopathic VT are more likely to be hospitalized and more likely to be referred for radiofrequency catheter ablation, while patients with the benign form of idiopathic VT are more likely to be treated conservatively as outpatients; therefore, the true frequency of the malignant form of idiopathic VT originating from RVOT is unknown but is much lower than 16%. Several patients with idiopathic VF have been reported as case reports, in which the initiating VPCs originated from RVOT could be successfully abolished by radiofrequency catheter ablation.17–19

How can we distinguish the malignant form from the benign form of idiopathic VT originating from RVOT?

Malignant ventricular arrhythmias, VF, and/or polymorphic VTs are sometimes associated with idiopathic VT or VPCs, which originate from RVOT. It is of particular importance to distinguish the malignant form from the benign form of idiopathic VT originating from RVOT, since the malignant form of idiopathic VT or VPCs often leads to unexpected sudden cardiac death.11–13

Several differences in ECG characteristics have been reported between malignant and benign forms of idiopathic VT. Some reports have suggested a relatively short CI of initiating VPCs, which arise from RVOT and result in malignant VF or polymorphic VT. Haissaguerre et al11 divided 27 patients with idiopathic VF into two groups according to the origin of the initiating VPCs: VPCs elicited from the Purkinje conduction system in 23 patients and those originating from the myocardium at RVOT in four patients. They compared several ECG parameters of initiating VPCs between groups, although these parameters were not compared with the benign form of idiopathic VT arising from RVOT. The CIs of the initiating VPCs were short in both groups but were longer in idiopathic VF originating from RVOT than from the Purkinje system (355 ± 30 vs. 280 ± 26 ms; P = .01; Table 1). In the three patients with malignant RVOT VT reported by Viskin and coworkers,12 the CI of VPCs in three patients (340 ± 30 ms) was longer than that of VPCs in idiopathic VF (300 ± 40 ms) but shorter than that of VPCs in benign RVOT VT (427 ± 76 ms; Table 1). Moreover, when both monomorphic and polymorphic VT were recorded in the same patient, the CI leading to polymorphic VT was shorter than that leading to monomorphic VT. In the report by Noda and coworkers,13 the CI of initiating VPCs in malignant RVOT VT was also short compared with the CI in benign RVOT VT (409 ± 62 vs. 428 ± 65 ms), although this did not reach statistical significance (Table 1). Thus, the available data suggest that the shorter CI of initiating VPCs correlates with the more malignant form of RVOT VT but that a cutoff value that would reliably differentiate malignant RVOT VT from benign RVOT VT remains to be defined. Moreover, long CI does not necessarily guarantee absence of risk.

The average QRS duration of the initiating VPCs originating from the RVOT in the malignant form of RVOT VT was reported to be 145 ± 12 ms by Haissaguerre et al11 and

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Figure 2 A: Polymorphic VT originating from RVOT in the malignant group on monitoring ECG. B: Monomorphic VT observed in the same malignant group patient as shown in panel A. C: Monomorphic VT originating from RVOT in the benign group. Note that the CL of monomorphic VT in the malignant group patient (280 ms) in panel B was longer than that of polymorphic VT in the same malignant group patient (250 ms) in panel A; however, it was shorter than that of monomorphic VT in the benign group (330 ms) in panel C.
148 ± 8 ms by Noda et al. It was longer than that in the idiopathic VF of Purkinje origin reported by Haissaguerre et al (145 ± 12 vs. 126 ± 18 ms; P = .04) and also slightly but significantly longer than that in the benign form of RVOT VT reported by Noda et al (148 ± 8 vs. 142 ± 12 ms; P = .03).

On the other hand, Noda et al suggested a significant difference of the cycle length (CL) of VT between malignant and benign forms of RVOT VT (245 ± 28 vs. 328 ± 65 ms; P < .0001) (Table 1); however, it was not surprising that the CL of polymorphic VT in the malignant group was shorter than that of monomorphic VT in the benign group. Therefore, we further analyzed the CL of monomorphic VT between malignant and benign groups. Among 16 patients with the malignant form of RVOT VT, both monomorphic RVOT VT and polymorphic RVOT VT were recorded in seven patients. The CL of monomorphic VT recorded in the seven malignant RVOT VT group patients was still significantly shorter than the CL of monomorphic VT in the 85 benign RVOT VT group patients (273 ± 23 vs. 328 ± 65 ms; P = .0001; Figure 2). Among the seven malignant RVOT VT group patients, the CL of monomorphic VT tended to be longer than that of polymorphic VT (273 ± 23 vs. 241 ± 36 ms; P = .08). Moreover, a previous history of syncope with malignant characteristics was more frequently observed in the seven malignant RVOT VT group patients than in the 85 benign RVOT VT group patients (5/7 vs. 15/85; P = .005). These data suggest that a shorter CL during monomorphic VT, when present, as well as a history of syncope with malignant characteristics, may be a predictor of the coexistence of malignant VF or polymorphic VT in patients with idiopathic VT originating from RVOT. In consideration of the available evidence, Holter or monitor ECG to record spontaneous episodes of RVOT VT and obtaining detailed previous history of syncope with malignant characteristics are useful to differentiate the malignant form from the benign form of RVOT VT.

Possible mechanism of the malignant form of idiopathic VT originating from RVOT

Although the mechanism of benign idiopathic monomorphic VT arising from RVOT is considered to be triggered activity, that of the malignant form of idiopathic RVOT VT is unknown because of less investigation of electrophysiologic characteristics during the ablation procedure. Among the 16 patients with malignant idiopathic RVOT VT reported by Noda and coworkers, programmed electrical stimulations induced VF in one patient and polymorphic VT in two patients. We also conducted rapid pacing from the origin of initiating VPCs after radiofrequency catheter ablation and could reproduce polymorphic morphological changes in the QRS configuration in two of seven patients (Figure 3). It is speculated that functional block and/or delayed conduction by rapid firing due to triggered activity or microreentry arising from a single focus led to chaotic ventricular conduction, thus causing VF and/or polymorphic VT. However, it is also speculated that rapid firing from close multiple foci one after another produces polymorphic morphological changes in the QRS configuration, since other VPCs with slightly different QRS morphology often appeared after eliminating the initial target VPCs by radiofrequency ablation.

Therapy and follow-up

Similar to the benign form of idiopathic VT originating from RVOT, radiofrequency catheter ablation was conducted to prevent VF or polymorphic VT in patients with the malignant form of idiopathic RVOT VT. Precise mapping and catheter ablation for the malignant form of RVOT VT require a clear-cut trigger in the form of frequent VPCs, just as for the benign form of RVOT VT. Haissaguerre et al performed catheter ablation in four patients with idiopathic VT elicited from RVOT. Late recurrence of VPCs with the same morphology as preablation was observed in one patient; however, sudden cardiac death, syncope, or recurrence of VF were not reported. In the three patients with the malignant form of idiopathic RVOT VT reported by Viskin et al, radiofrequency catheter ablation was conducted in only one patient, an implantable defibrillator-cardioverter (ICD) was implanted in the remaining two patients, and all three patients were reported to be free of arrhythmia recurrence. Noda et al performed radiofrequency catheter ablation in all 16 patients with the malignant form of idiopathic VT arising from RVOT. The ICD was implanted in one patient with induced VF after ablation, and β-blocker was used in four patients with partially successful ablation. During 106 months of follow-up, no recurrence of syncope, VF, or cardiac arrest was observed. How-

![Figure 3 Polymorphic changes of the QRS complex on ECG leads I, II, V1, and V5 during rapid pacing in a patient with the malignant form of idiopathic VT originating from RVOT. The morphological changes were induced by rapid pacing from the origin of the initiating VPC, which was confirmed by the efficacy of radiofrequency catheter ablation. Reproduced from reference 13 with permission.](image-url)
ever, among our series of the 16 patients with malignant idiopathic RVOT VT, a significant sign of ARVD (aneurysmal formation of the RV mid to apex, dilatation of the RVOT) was developed in one patient 10 years later after catheter ablation. These data suggest that radiofrequency catheter ablation seems to be effective to cure the malignant form of idiopathic VT arising from RVOT; however, a backup of ICD implantation is required in patients with the malignant form of idiopathic RVOT VT, especially in those with documented VF or cardiac arrest, since the feasibility of ablation has been demonstrated in small series of patients in expert centers and long-term follow-up data of catheter ablation are lacking. Moreover, our data indicate that careful morphological follow-up with cardiac imaging is also needed for early detection of progression to ARVD in some patients with the malignant form of benign-looking RVOT VT.

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References