Right Ventricular Outflow Tract Arrhythmia From Single Ectopic Beats To Arrhythmogenic Right Ventricular Cardiomyopathy

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Received 14/3/2009, reviewed 30/3/2009, accepted 1/4/2009
DOI:10.5083/ecdcip.17560993.03

During our clinical practice when we see a patient (especially young) with ectopic Premature Ventricular Beats (PVC) from Right Ventricular Outflow Tract (RVOT), we should think about an ECG pattern of the arrhythmologic disease. Although it may vary from benign RVOT extra beats or could represent an idiopathic ventricular tachycardia in a structurally normal heart. Seldom it may be the only sign of arrhythmogenic right ventricular dysplasia (ARVD) a very complex disease that related with high incidence of sudden cardiac death (SCD) [3]. Careful and close work-up and risk stratification is necessary for all patients presenting with PVCs from RVOT.

Monomorphic RVOT extra beats and RVOT VT appear to be on a continuum of the same process. RVOT extra beats on 12 lead standard ECG are characterised by ventricular ectopy with left bundle branch block (LBBB) morphology and inferiorly directed QRS axis.

Patients with RVOT PVCs, ideopathic RVOT VT or ARVD have a wide spectrum of symptoms, ranging from none, to palpitations, lightheadedness, dyspnea, presyncope, or syncope.

Figure 1.
An example of VT originated from RVOT.
Note the presence of LBBB (weighty S waves on lead V1 & aVR and R waves on Lead V6 & II) and Inferior QRS axis ( tall R waves on the inferior leads II; III; aVF )

The ideopathic VTs originated from RVOT usually carry only a low risk for syncope or SCD in the presence of structurally normal heart and myocardium. In contrast ARVD is a disease of the heart muscle associated with life-threatening ventricular arrhythmias and sudden death.

It is characterised by structural and functional abnormalities of the right ventricle caused by the replacement of the myocardium by fatty and fibrous tissue.

The disease is progressive and at some stages it may cause also dilatation and dysfunction of the right ventricle and electrical instability, ventricular arrhythmia of right ventricular origin, which eventually can lead to heart failure and sudden death. The sites of involvement of anatomic abnormalities are found in the so-called triangle of dysplasia (the right ventricular subtricuspid areas, the apex and the infundibulum) [1].

ARVD is an inherited disease, typically inherited as an autosomal dominant trait with variable penetrance and incomplete expression [2]. There is an autosomal recessive variant associated with palmoplantar keratosis and wally hair named Naxos disease. The prevalence in the general population is approximately from 1:2500 to 1:5000. It occurs in young adults with a male to female ratio of 2,7/1.

After hypertrophic heart disease, it is the number one cause of sudden cardiac death in young people. And it accounts for 5% to 10% of unexplained sudden cardiac deaths in individuals less than 65 years [3]. It depends on geographic circumstances as well as the methods of autopsy screening for young SCD victims that vary from country to country.
Differential Diagnosis:

Even in a case of documented VT with LBBB and inferior QRS axis the diagnosis of an idiopathic RVOT VT is made by exclusion of ARVC or any other structural heart disease.

According to the European Society of Cardiology (ESC) Task Force Report [4], the diagnosis is based on the detection of structural, histological, electrocardiographic, arrhythmic and genetic factors.

There are several ECG features in the criteria diagnosis of ARVD:

- T wave inversions in V1 through V3 (minor diagnostic criterion, but one of most common ECG abnormality present in 85% of patients [5])
- QRS duration = 110 ms in V1 through V3
- Epsilon wave (electric potentials after the end of the QRS complex). It is a major diagnostic criterion found in up to 30% of cases of ARVD.
- Other ECG markers of ARVD have been reported: QRS and QT dispersion, parietal block defined as a QRS duration in leads V1 through V3 that exceeds the QRS duration in lead V6 by more than 25 msec, a prolonged S-wave upstroke in V1 through V3 about 55 msec (it was seen as the most prevalent ECG feature and presents in 95% of ARVD cases)
- Echocardiography is the most important initial diagnostic approach and should be performed in any patient suspected of having ARVD. In the beginning of the disease the Echocardiographic yield is rather small and usually normal ECHO pattern or minimal abnormalities can be found, that is not exclude the diagnosis [6]. Principal findings during the ECHO are:
  - right ventricular dilation and hypokinesia
  - isolated dilatation of the right ventricular outflow tract
  - increased reflectivity of the moderator band
  - end-diastolic aneurysms
  - akinesis-dyskinesis of the infero-basal segment and the right ventricular apex
  - prominent apical trabeculae.

Most valuable tests are computed tomography and cardiovascular magnetic resonance imaging

Magnetic resonance (MR) is an excellent tool for visualising the right ventricle. MR can also be used to assess both systolic and diastolic function. Several studies have addressed the presence of right ventricular diastolic dysfunction as an early marker of the disease [7].

The typical criteria that can be demonstrated with MR are:

- presence of high-signal intensity areas indicating the substitution of myocardium by fat (major criterion)
- fibrofatty replacement which leads to diffuse thinning of the right ventricular myocardium (major criterion)
- aneurysm of the right ventricle and right ventricular outflow tract (major criterion)
- dilatation of the right ventricle and right ventricular outflow tract (when severe, major criterion; when mild, minor criterion)
- regional contraction abnormalities (minor criterion)
- global systolic dysfunction (major criterion) and global diastolic dysfunction (minor criterion).

Computed tomography is capable to diagnose patients with ARVD. Dery et al [8], were the first to demonstrate a dilated hypokinetic right ventricle in a patient with ARVD.

Findings of ARVD on electron-beam computed tomography are [9]:

- the presence of epicardial fat or intramyocardial fat deposits
- conspicuous trabeculations with low attenuation
- dilated hypokinetic right ventricle
- scalloped appearance of the right ventricular wall.

Computed tomography is not the optional imaging modality for initial screening due to high adiation burden.
Right ventricular contrast angiography

This technique is considered the reference standard for the diagnosis of ARVD. It consists of akinetic-dyskinetic areas localised in the anatomic triangle of dysplasia. However, due to an invasive technique, X-ray exposure, this method is not widely used in routine diagnostic work-up but it is widely used during EP study of RVOT VT’s.

However, diagnosis of ARVD must be made based on Task Force criteria and not on structural abnormalities only. Endomyocardial biopsy is controversial because of the segmental nature of the disease and the samples are usually obtained from the septum. Complications such as tamponade and perforation can occur during procedure. Genetic analysis is useful tool for diagnosis of ARVD appears to be mandatory for patients with family history of sudden cardiac death in <35 years.

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Global or regional dysfunction and structural alterations</td>
<td>(1) Severe dilatation and reduction in the right ventricular ejection fraction with no or only mild left ventricular impairment or (2) localised right ventricular aneurysms (akinetic-dyskinetic areas of diastolic bulging)</td>
<td>(1) Minor global right ventricular dilatation or ejection fraction reduction with normal left ventricle, (2) mild segmental dilatation of the right ventricle, or (3) regional right ventricular hypokinesia</td>
</tr>
<tr>
<td>Repolarisation of abnormalities</td>
<td>None</td>
<td>Inverted T waves in the right precordial leads beyond V1 (patient &gt;12 y, in the absence of a right bundle branch block)</td>
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<tr>
<td>Depolarisation or conduction abnormalities</td>
<td>Epsilon waves or localised prolongation (110 ms) of the QRS complex in precordial leads (V1, V2, or V3)</td>
<td>Late potentials (signal-averaged electrocardiography)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Sustained left bundle-branch-block type of VT (as determined with electrocardiography, Holter monitoring, or exercise testing)</td>
<td>Frequent ventricular extrasystoles with left bundle-branch-block morphology (&gt;1000 per 24 h, as seen with Holter monitoring)</td>
</tr>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
<td>(1) Family history of premature sudden death (&lt;35 y) caused by suspected RVD or (2) family history (clinical diagnosis based on current criteria)</td>
</tr>
<tr>
<td>Tissue characterisation of the RV myocardium</td>
<td>Fatty infiltration of the RV myocardium</td>
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The Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology (ESC) and the Task Force of the Scientific Council on Cardiomyopathies of the World Heart Federation (Geneva, Switzerland) proposed standardized diagnostic criteria.

The diagnosis of ARVD is based on the presence of major and minor criteria encompassing structural, histologic, electrocardiographic, arrhythmic, and genetic factors. To fulfill the appropriate criteria for ARVD, the patient’s condition must meet 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria (see Table 1, below).
ARVC is a progressive disease. Four phases have been described in the disease:

- silent phase
- appearance of arrhythmias
- appearance of structural anomalies
- heart failure

It leads to RV failure if sudden death does not occur before. The death rate is approximate 2.5% per year [5].

There is no curative treatment. The aim is to detect patients at high risk and prevent complications.

Unfortunately, SCD is frequently the first manifestation of the disease. The annual incidence of SCD has varied, ranging from 0.08% to 9%. SCD occurs relatively frequently during exercise or stress, but SCD is not uncommon with no apparent provocation. RV dilation, precordial repolarisation abnormalities, LV involvement associated with SCD. [12] SCD occurs not only in individuals with visible RV abnormalities, but in individuals with only microscopic abnormalities.

Recommendations for ARVC from ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death:

**Class I**

ICD implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1y. (Level of evidence: B)

**Class IIa**

1. ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, 1 or more affected family member with SCD, or undiagnosed syncpe when VT or VF has not been exclude as the cause of syncpe, who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1y. (Level of evidence: C)

2. Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with ARVC when ICD implantation is not feasible. (Level of evidence: C)

3. Ablation can be useful as adjunctive therapy in management of patient with ARVC with recurrent VT, despite optimal antiarrhythmic drug therapy. (Level of evidence: C)

**Class IIb**

EP testing might be useful for risk assessment of SCD in patients with ARVC. (Level of evidence: C)

Pharmacological agents as first choice are ACEI, anticoagulants, diuretics and antiarrhythmic agents as sotalol, verapamil, betablockers, amiodarone, flecainide. Surgery, which consist ventriculotomy and disconnection of the RV free wall, shuld be consider as option in refracter patients. If severe terminal heart failure occur the last option is cardiac transplantation.

If ARVC or any other structural heart disease (e.g. tetralogy of Fallot) have been exclude, the patient most likely has an idiopathic RVOT-VT. Exercise stress testing is used frequently to initiate and evaluate RVOT VT [13] ECG and echocardiogram in sinus rhythm are usually normal, as is coronary angiography.

MRI may show abnormalities of the RV in up to 70% of patients, including focal thinning, diminished systolic wall thickening, and abnormal wall motion [14]. RVOT-ectopies are common, malignant RVOT arrhythmias are rare. Patients with a malignant course were not different, at the time of presentation, from patients with benign RVOT-VT [15]. Triggered activity, rather than reentry or enhanced automaticity, as the cause of RVOT VT is evidenced by termination with administration of adenosine and inability to entrain. The tachycardia may be inducible.
Recommending aggressive therapy for all patients with RVOT-ectopy is not clear, because because therapy for RVOT arrhythmias is not without risk.

Acute termination of RVOT VT can be achieved by vagal maneuver or intravenous administration of adenosine, 6 mg, which can be titrated up to 24 mg as needed. Intravenous verapamil, 10 mg, given over 1 minute is an alternative, provided the patient has adequate blood pressure and has a previously established diagnosis of verapamil-sensitive VT. Lidocaine also may be effective in some cases. Hemodynamic instability warrants emergent cardioversion.

Long-term treatment options for RVOT VT include medical therapy or RF ablation. Medications, including beta-blockers or verapamil (diltiazem is equally effective), have a 25% to 50% rate of efficacy. Alternative therapy includes class IA, class IC, and class III agents including amiodarone [16], RF ablation now has cure rates of 90%, [17] which makes it a preferable option, given the young age of patients with RVOT VT.

Radiofrequency ablation should be recommended early, rather than late, for patients with these high-risk characteristics:

1. a history of syncope [15]
2. very fast VT (because ventricular rates >230 beats/min are associated with polymorphic VT) [9]
3. extremely frequent ectopy (>20,000 extrasystoles/day) because such degree of ectopy causes cardiac desynchronization and may eventually lead to cardiac dilatation [18]
4. ventricular ectopy with short coupling interval (because the shorter the coupling interval, the higher the probability for polymorphic arrhythmias), noting that the absence of short coupling intervals is no guarantee against polymorphic RVOT-VT [15], [18].

More than 90% of patients, who have adequate target material for ablation have a successful outcome, defined as lack of spontaneous arrhythmia episodes in the absence of adjunctive medical therapy. Patients with recurrent episodes after an apparently successful outcome may have repeat ablation, which is usually successful.

Potential complications of ablation occur in <1% of cases and include myocardial perforation with cardiac tamponade due to catheter manipulation during mapping or rupture during ablation in the RVOT, and very rarely heart block. Excessive ablation in the septal portion of the RVOT can result in injury to the left anterior descending or left main coronary arteries with resultant myocardial infarction. Death from the procedure is extremely rare [19].

As a class IIa recommendation (with level of evidence: C) ICD implantation can be effective therapy for the termination of sustained VT in patients with normal or near normal ventricular function and no structural heart disease who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year [12].
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