Diagnostic Value of Isoproterenol Testing in Arrhythmogenic Right Ventricular Cardiomyopathy

Arnaud Denis, MD; Frédéric Sacher, MD, PhD; Nicolas Derval, MD; Han. S. Lim, MBBS; Hubert Cochet, MD, PhD; Ashok J. Shah, MD; Matthew Daly, MBChB; Xavier Pillois, PhD; Khaled Ramoul, MD; Yuki Komatsu, MD; Adlane Zemmoura, MD; Sana Amraoui, MD; Philippe Ritter, MD; Sylvain Ploux, MD; Pierre Bordachar, MD, PhD; Mélèze Hocini, MD; Pierre Jaïs, MD; Michel Haïssaguerre, MD

Background—Although the Task Force Criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) have recently been updated, the diagnosis remains challenging in the early stages. The aim of this study was to evaluate the diagnostic value of β-adrenergic stimulation in ARVC.

Methods and Results—We evaluated 412 consecutive patients (213 men, age 41.5±16 years) referred for premature ventricular contractions evaluation or suspected ARVC. Isoproterenol testing was performed with continuous infusion of isoproterenol (45 μg/min) for 3 minutes. It was considered positive if there were either (1) polymorphic premature ventricular contractions with ≥1 couplet or (2) sustained or nonsustained ventricular tachycardia with left bundle branch block excluding right ventricular outflow tract ventricular tachycardia. ARVC was diagnosed in 35 patients at initial evaluation (23 men, aged 42±15 years). Isoproterenol testing was positive in 32 of 35 (91.4%) patients with ARVC and in 42 of 377 (11.1%) patients without ARVC (P<0.0001). Sensitivity, specificity, positive, and negative predictive values of isoproterenol testing to diagnose ARVC were 91.4%, 88.9%, 43.2%, and 99.1%, respectively. During a mean follow-up period of 5.6±4.4 years, 6 additional patients met diagnostic criteria for ARVC. Importantly, initial isoproterenol testing was positive in 6 of 6 (100%) of these patients. Survival free from ARVC diagnosis was significantly lower in the positive isoproterenol group than in the negative isoproterenol group (P<0.0001, exact log-rank test).

Conclusions—Ventricular arrhythmogenicity during isoproterenol testing is highly sensitive (sensitivity, 91.4%) for the diagnosis of ARVC, particularly in its early stages. (Circ Arrhythm Electrophysiol. 2014;7:590-597.)

Key Words: arrhythmogenic right ventricular dysplasia ▶ diagnosis ▶ isoproterenol ▶ tachycardia, ventricular

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement of the right ventricular myocardium.1 Various estimates place the prevalence of this disease between 1 in 2000 and 1 in 5000.2,3 Mutations identified in patients with ARVC are predominantly localized in genes encoding desmosomal proteins4–9 but may also affect the cardiac ryanodine receptor gene (ryanodine receptor 2), which gives rise to either ARVC type 2 or catecholaminergic polymorphic ventricular tachycardia (VT).10,11

Editorial see p 565
Clinical Perspective on p 597

The clinical diagnosis of ARVC is often difficult in the early stage of the disease because of the lack of specific diagnostic tools and incomplete penetrance of the disease.12 Morphological abnormalities, which can usually be localized in the triangle of dysplasia, may be absent particularly at the initial evaluation, in the early stages of the disease. Cardiac MRI was considered normal or borderline in 14% and 26%, respectively, of patients newly identified with ARVC13 and 36% of patients with ARVC with a history of sustained ventricular arrhythmias, and cardiac arrest did not have major or minor criteria on cardiac imaging (MRI or echocardiogram).14 The diagnosis of ARVC is based on the1994 Task Force Criteria (TFC),15 which were updated in 2010.16 Although correct identification may be straightforward in severe and diffuse ARVC cases, it remains challenging in patients presenting in the early stages. Early detection is crucial because ARVC can result in sudden cardiac death, especially in young people during exertion.17–20 Endurance training provokes right ventricular arrhythmias in a murine model of reduced plakoglobin expression,21 and adrenergic stimulation is well known to have a major role in induction of ventricular arrhythmias in ARVC.22 We hypothesized that isoproterenol, a commonly used nonselective β-adrenergic agonist, (1) may unmask catecholamine sensitive ventricular arrhythmias and (2) serve as an additional diagnostic tool to provide early identification of ARVC.
Methods

Study Design and Population

All patients referred to our institution between 2000 and 2013 for either (1) evaluation of premature ventricular contraction (PVC) or (2) suspicion for ARVC were included in this study, provided they had normal left ventricular function. Between 2000 and 2010, cases were analyzed retrospectively, whereas patients were prospectively recruited from June 2010 to 2013. All patients underwent isoproterenol testing because this test is performed routinely for the evaluation of catecholamine-related arrhythmogenic risk. Patients with an established diagnosis of ARVC referred for further management, such as VT ablation, were excluded from this study (n=19), as were patients with other identified structural heart disease. Patients on amiodarone were also excluded as the drug may modify the response to isoproterenol. Detailed personal and family history, 12-lead ECG recordings, exercise test, 24-hour Holter monitoring, signal-averaged ECG, 2-dimensional transthoracic echocardiography, cardiac MRI, right ventricular (RV) angiography, and genetic analysis, if performed, were obtained for every patient. This study was approved by the institutional review committee, and the subjects gave informed consent.

In the first phase of the study, we hypothesized that isoproterenol testing may unmask catecholamine sensitive ventricular arrhythmias in patients with ARVC. The diagnostic value of isoproterenol testing in ARVC was compared with diagnoses based on the revised TFC.16

In the second phase of the study, we hypothesized that isoproterenol testing could serve as an additional tool to provide early diagnosis of ARVC. Therefore, all patients were followed up, and additional cases of ARVC diagnosed under the revised TFC were recorded during the follow-up period. The usefulness of isoproterenol testing for earlier identification of ARVC was further examined in this setting. The follow-up included outpatient consultation and hospitalization in our center and outpatient consultation with the referring cardiologist every 6 months. A repeated complete evaluation was performed in borderline patients and in patients who had changes in clinical or ECG characteristics. Follow-up duration was defined as the period between the initial isoproterenol test and the last medical follow-up.

Table 1. Clinical Characteristics of the Study Population at Inclusion

<table>
<thead>
<tr>
<th></th>
<th>ARVC</th>
<th>No ARVC</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>41.9±14.6</td>
<td>41.4±16.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>23 (65.7)</td>
<td>190 (50.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of major criteria, mean±SD</td>
<td>1.4±0.8</td>
<td>0.1±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of minor criteria, mean±SD</td>
<td>2.4±0.8</td>
<td>1.1±0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Familial history, n (%)</td>
<td>8 (22.9)</td>
<td>11 (2.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Initial symptoms,† n (%)</td>
<td>3 (8.6)</td>
<td>27 (7.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>27 (77.1)</td>
<td>230 (61)</td>
<td>0.06</td>
</tr>
<tr>
<td>Palpitations</td>
<td>12 (34.3)</td>
<td>146 (38.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (25.7)</td>
<td>53 (14.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (34.3)</td>
<td>43 (11.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aborted SCD</td>
<td>3 (8.6)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular arrhythmia at rest,‡ n (%)</td>
<td>11 (32.4)</td>
<td>282 (74.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Monomorphic PVC</td>
<td>15 (44.1)</td>
<td>24 (6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>8 (23.5)</td>
<td>54 (14.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>11 (31.4)</td>
<td>15 (4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; PVC, premature ventricular contraction; SCD, sudden cardiac death; and VT, ventricular tachycardia.

Methods

Study Design and Population

All patients referred to our institution between 2000 and 2013 for either (1) evaluation of premature ventricular contraction (PVC) or (2) suspicion for ARVC were included in this study, provided they had normal left ventricular function. Between 2000 and 2010, cases were analyzed retrospectively, whereas patients were prospectively recruited from June 2010 to 2013. All patients underwent isoproterenol testing because this test is performed routinely for the evaluation of catecholamine-related arrhythmogenic risk. Patients with an established diagnosis of ARVC referred for further management, such as VT ablation, were excluded from this study (n=19), as were patients with other identified structural heart disease. Patients on amiodarone were also excluded as the drug may modify the response to isoproterenol. Detailed personal and family history, 12-lead ECG recordings, exercise test, 24-hour Holter monitoring, signal-averaged ECG, 2-dimensional transthoracic echocardiography, cardiac MRI, right ventricular (RV) angiography, and genetic analysis, if performed, were obtained for every patient. This study was approved by the institutional review committee, and the subjects gave informed consent.

In the first phase of the study, we hypothesized that isoproterenol testing may unmask catecholamine sensitive ventricular arrhythmias in patients with ARVC. The diagnostic value of isoproterenol testing in ARVC was compared with diagnoses based on the revised TFC.16

In the second phase of the study, we hypothesized that isoproterenol testing could serve as an additional tool to provide early diagnosis of ARVC. Therefore, all patients were followed up, and additional cases of ARVC diagnosed under the revised TFC were recorded during the follow-up period. The usefulness of isoproterenol testing for earlier identification of ARVC was further examined in this setting. The follow-up included outpatient consultation and hospitalization in our center and outpatient consultation with the referring cardiologist every 6 months. A repeated complete evaluation was performed in borderline patients and in patients who had changes in clinical or ECG characteristics. Follow-up duration was defined as the period between the initial isoproterenol test and the last medical follow-up.

Table 2. Results of Isoproterenol Testing Based on the Revised TFC at Inclusion

<table>
<thead>
<tr>
<th></th>
<th>ARVC</th>
<th>No ARVC</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive isoproterenol testing,† n (%)</td>
<td>32 (91.4)</td>
<td>42 (11.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polymorphic PVC and couplet(s)</td>
<td>5 (14.3)</td>
<td>22 (5.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Monomorphic nonsustained VT, non-RVOT morphology</td>
<td>1 (2.9)</td>
<td>1 (0.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Monomorphic sustained VT, non-RVOT morphology</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Polymorphic nonsustained VT</td>
<td>17 (48.6)</td>
<td>13 (3.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polymorphic sustained VT</td>
<td>9 (25.7)</td>
<td>6 (1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Negative isoproterenol testing</td>
<td>0 (0)</td>
<td>16 (4.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Monomorphic nonsustained VT, RVOT morphology</td>
<td>0 (0)</td>
<td>11 (2.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Monomorphic sustained VT, RVOT morphology</td>
<td>0 (0)</td>
<td>11 (2.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Maximal heart rate, mean±SD, bpm</td>
<td>145±18</td>
<td>152±19</td>
<td>0.03</td>
</tr>
<tr>
<td>β-Blocker administration</td>
<td>7 (20)</td>
<td>9 (2.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; bpm, beats per minute; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; TFC, task force criteria; and VT, ventricular tachycardia.

*Pearson χ2 test or Fisher exact test (if n<5) was used for categorical variables, and Student t test was used for continuous variables.

†Positive criteria for isoproterenol testing are mutually exclusive and presented in a progressive order of arrhythmia severity.
Isoproterenol Testing

Isoproterenol testing was performed after withdrawal of β-blockers, calcium channel blockers, and other antiarrhythmic agents for ≥5 half-lives. Equipment for cardiopulmonary resuscitation was readily accessible in the room during the test. A continuous infusion of isoproterenol (infusion speed 45 micrograms/min) was administered for 3 minutes, regardless of heart rate. The 12-lead ECG (recorded at 25 mm/s and 10 mm/mV) was continuously recorded from the beginning of infusion ≤10 minutes after the cessation of infusion.

The test was considered positive if either (1) polymorphic (≥3 morphologies) PVCs and ≥1 couplet or (2) sustained or nonsustained monomorphic or polymorphic VT with left bundle branch block morphology predominance (with the exclusion of right ventricular outflow tract [RVOT] VT) occurred during the test or within 10 minutes from the end of infusion. Positive criteria for isoproterenol testing are mutually exclusive, and the most severe ventricular arrhythmia was retained. The infusion was immediately stopped if the test was positive, and, in cases of VT, a β-blocker (atenolol 5 mg for 1 minute) was injected intravenously.

Maximal heart rate, arrhythmia type, rate and morphology, and the occurrence of vasovagal response were documented. Sustained VT was defined as a ventricular rhythm faster than 120 beats per minute (bpm) lasting ≥30 seconds. Nonsustained VT was defined as a ventricular rhythm faster than 120 bpm lasting for ≥3 beats that spontaneously resolves in <30 seconds. Polymorphic PVCs were defined as PVCs with ≥3 different morphologies. A vasovagal response was defined as occurrence of an accelerated idioventricular rhythm (ectopic ventricular rhythm with ≥3 consecutive ventricular beats at the rate of 40–120 bpm) or abrupt heart rate reduction in association with vasovagal symptoms.

Statistical Analysis

Continuous variables were expressed as mean±SD, and categorical data expressed as number and percentages. The
distribution of continuous variables was examined for normality using the Kolmogorov–Smirnov test and histogram plots. Continuous variables were compared using the Student t test. Categorical variables were compared using the Pearson \( \chi^2 \) test. Where the expected value was \(<5\), the Fisher exact test was used instead. The sensitivity and specificity of isoproterenol testing were evaluated compared with the revised TFC at study inclusion and presented with 95% confidence intervals. For the second phase of the study, patients without the initial diagnosis of ARVC at study inclusion were divided into positive and negative isoproterenol testing groups. Event free survival (ARVC diagnosis during follow-up) was estimated by the Kaplan–Meier method with comparison made using the exact log-rank test. A value of \( P<0.05 \) was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, IL) and StatXact version 10 (Cambridge, MA).

Results

Phase 1: Diagnostic Value of Isoproterenol Testing at Initial Evaluation

Study Population

Four hundred and twelve patients (213 [51.7%] men, age 41.5±16 years) were included in the study. ARVC was diagnosed in 35 patients at initial evaluation. Clinical characteristics are summarized in Table 1.

Isoproterenol Testing

The maximal sinus rhythm heart rate during isoproterenol testing (Figure 1) was 152±19 bpm, 85±11% of the age-adjusted maximum heart rate (145±18 bpm in patients with ARVC and 152±19 bpm in patients without ARVC, \( P=0.03 \), 81±10% and 86±11% of the age-adjusted maximum heart rate, respectively). This significant difference between the 2 groups was explained by the induction of ventricular arrhythmias in patients with ARVC prompting termination of the test before reaching maximal sinus rhythm heart rate.

Isoproterenol testing was positive in 74 of 412 (18%) patients. It was positive in 32 of 35 (91.4%) patients in whom the diagnosis of ARVC was established and in 42 of 377 (11.1%) patients without ARVC \( (P<0.0001) \). The main results of isoproterenol testing are summarized in Table 2.

Ventricular arrhythmias induced by isoproterenol testing in patients with ARVC consisted of (1) polymorphic PVCs and \( \geq 1 \) couplet, 5 of 35 (14.3%) versus 22 of 377 (5.8%) in patients without ARVC \( (P=0.05) \); (2) monomorphic nonsustained VT, non-RVOT morphology, 1 of 35 (2.9%) versus 1 of 377 (0.3%) in patients without ARVC; (3) polymorphic nonsustained VT, 17 of 35 (48.6%) versus 13 of 377 (3.4%) in patients without ARVC \( (P<0.0001) \); and (4) sustained polymorphic VT, 9 of 35 (25.7%) versus 6 of 377 (1.6%) in patients without ARVC \( (P<0.0001) \) (Figure 2).

Based on these results, the diagnostic value of isoproterenol testing in ARVC was compared with diagnoses based on the revised TFC\(^{\text{a}} \) at inclusion. Sensitivity, specificity, positive, and negative predictive values of isoproterenol testing to diagnose ARVC were 91.4% (95% confidence interval, 90.5–100), 88.9% (95% confidence interval, 85.7–92), 43.2%, and 99.1%, respectively (Table 3).

Monomorphic sustained or nonsustained RVOT VT (without any other ventricular arrhythmias) were observed in 0 of 35 (0%) patients with ARVC versus 27 of 377 (7.2%) patients without ARVC. After a mean follow-up of 6.4±2.2 years (1 patient lost to follow-up), none of these patients developed ARVC and 12 underwent RVOT VT ablation.

The average sinus rhythm heart rate at the onset of ventricular arrhythmias during isoproterenol testing was 131±24 bpm (median 135 bpm, 73±11% of the age-adjusted maximum heart rate) in patients with ARVC.

Sixteen tests (3.9%) were interrupted before the end of 3 minutes because of VT induction. No syncope was observed, and \( \beta \)-blocker injection restored sinus rhythm without need for electric cardioversion.

A vasovagal response occurred in 33 (8%) tests; of these an accelerated idioventricular rhythm was seen in 19 patients (57.6%) and a decrease in heart rate during the test with vasovagal symptoms in 14 patients (42.4%). One patient with a previous history of vagal hypertonia experienced a vasovagal syncope during isoproterenol testing (resolved with legs elevated).

Phase 2: Usefulness of Isoproterenol Testing for Early Identification of ARVC

During a mean follow-up period of 5.6±4.4 years (median, 5 years; interquartile range, 2.0–8.2), 6 additional patients from the initial non-ARVC group met diagnostic criteria for ARVC. Therefore, 41 patients (28 [68.3%] men, mean age at diagnosis 40±15 years) fulfilled TFC by the end of follow-up. Thirty of 41 (73.2%) patients with ARVC had genetic screening for ARVC mutations, in whom 10 patients had a mutation identified (9 Plakophilin-2 and 1 Desmocollin-2). Twenty-four of 371 (6.5%) patients without ARVC had genetic screening, and no patient had a mutation.

Isoproterenol Testing in Patients With ARVC Not Recognized at Initial Evaluation

The isoproterenol test performed at study inclusion was positive (1 polymorphic sustained VT, 3 polymorphic nonsustained VT, and 2 polymorphic PVCs with couplets) in all 6 patients who did not fulfill TFC at the initial evaluation but developed an overt form of ARVC later on. Diagnostic criteria at the initial evaluation and at the end of follow-up of these 6 patients are shown in Table 4. Two patients were identified by the occurrence of sustained VT during follow-up.

After a period of 4-year follow-up (mean, 7±3.7; median, 6.5 years), no additional patients met diagnostic criteria for ARVC. Hence, a Kaplan–Meier survival analysis was
**Table 4. Characteristics of Patients (n=6) With Positive Initial Isoproterenol Testing Not Fulfilling TFC but Subsequently Developing a Patent Form of ARVC**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, Age at Diagnosis</th>
<th>Polymorphic PVCs</th>
<th>Time From Isoproterenol Testing to Fulfillment to TFC</th>
<th>Initial Evaluation</th>
<th>Follow-Up</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Male, 30-y-old at diagnosis</td>
<td>Polymorphic PVCs with ≥1 couplet</td>
<td>4 y</td>
<td>Minor criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Sustained VT of LBB morphology with unknown axis</td>
<td>-Sustained VT of LBB morphology with superior axis</td>
<td>-VT ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-≥500 ventricular extrasystoles per 24 h (Holter)</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Inverted T wave in leads V1 and V2 in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td>-By MRI, regional RV dyskinesia, ratio of RV end-diastolic volume to BSA ≥110 mL/m² and RV ejection fraction ≤40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG</td>
<td>-Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>Female, 51-y-old at diagnosis</td>
<td>Polymorphic nonsustained VT</td>
<td>1 y</td>
<td>Major criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Familial history (clinical diagnosis based on present criteria)</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td>-Bisoprolol 6.25 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Minor criteria</td>
<td>-By MRI, regional RV dyskinesia and ratio of RV end-diastolic volume to BSA ≥110 mL/m²</td>
<td>-Ametole 50 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-≥500 ventricular extrasystoles per 24 h (Holter)</td>
<td>-Major criteria</td>
<td>-ICD implantation (syncope despite optimal medical therapy)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Male, 41 yr old at diagnosis</td>
<td>Polymorphic nonsustained VT</td>
<td>3 y</td>
<td>Minor criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Sustained VT of LBB morphology with unknown axis</td>
<td>-By MRI, regional RV dyskinesia and ratio of RV end-diastolic volume to BSA ≥110 mL/m²</td>
<td>-Nadolol 80 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG</td>
<td>-Major criteria</td>
<td>-Amiodarone 200 mg/d</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Male, 19-y-old at diagnosis</td>
<td>Polymorphic nonsustained VT</td>
<td>2 mo</td>
<td>Major criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-By MRI, regional RV dyskinesia and RV ejection fraction ≤40%</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td>-Nadolol 80 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Minor criteria</td>
<td>-≥500 ventricular extrasystoles per 24 h (Holter)</td>
<td>-VT ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R*, R', in V1, V2, V3 in the absence of complete right bundle branch block</td>
<td>-By MRI, regional RV dyskinesia and RV ejection fraction ≤40%</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>Male, 43-y-old at diagnosis</td>
<td>Polymorphic sustained VT</td>
<td>1 y</td>
<td>Minor criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-By MRI, regional RV dyskinesia and RV ejection fraction ≤40%</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td>-Amiodarone 200 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-≥500 ventricular extrasystoles per 24 h (Holter)</td>
<td>-Minor criteria</td>
<td>-VT ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG</td>
<td>-Sustained VT of RV outflow configuration, LBBB morphology with inferior axis</td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>Male, 14-y-old at diagnosis</td>
<td>Polymorphic PVCs with ≥1 couplet</td>
<td>3 mo</td>
<td>Major criteria</td>
<td>Major criteria</td>
<td>Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Familial history (clinical diagnosis based on present criteria)</td>
<td>-Inverted T wave in the right precordial leads (V1, V2, and V3) or beyond in individuals &gt;14 y of age (in the absence of complete RBBB)</td>
<td>-Nadolol 80 mg/d</td>
</tr>
</tbody>
</table>

ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; BBA, body surface area; ICD, implantable cardioverter defibrillator; LBB, left bundle branch; LBBB, left bundle branch block; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricle; RVOT, right ventricular outflow tract; SAECG, signal-averaged electrocardiography; TFC, task force criteria; and VT, ventricular tachycardia.
performed ≤4 years of follow-up, comparing patients with positive and negative isoproterenol testing at study inclusion that were categorized into the non-ARVC group at initial evaluation. Survival free from ARVC diagnosis was significantly lower in the positive isoproterenol testing group than in the negative isoproterenol testing group (P<0.0001 by the exact log-rank test; Figure 3).

Follow-Up of Patients Without ARVC With Positive Isoproterenol Testing

Thirty-six patients who had a positive isoproterenol test were not diagnosed of having ARVC according to the revised TFC at the end of follow-up. Of these patients, at mean follow-up of 5.7±5.1 years, 6 patients clinically suspected of having ARVC did not fulfill TFC (3 patients with 1 major and 1 minor criteria, 1 patient with 1 major criterion, and 3 patients with 3 minor criteria), 7 had catecholaminergic polymorphic VT, and no definite diagnosis could be made in 23 patients (17/23 had polymorphic PVCs with ≥1 couplet during isoproterenol testing). In the latter patients, 1 was on flecainide, 3 on sotalol, 11 on β-blockers, and 7 without antiarrhythmic medications at the end of follow-up. No syncope or cardiac arrest occurred during follow-up. One patient was lost to follow-up.

Discussion

Our data demonstrate that the arrhythmogenic response to isoproterenol testing is highly sensitive (sensitivity, 91.4%; and negative predictive value, 99.1%) in diagnosing ARVC and can be safely performed in a controlled environment.

These results are similar to a previous noncontrolled study, which suggested that isoproterenol testing may be useful for predicting ARVC during evaluation for PVCs or familial screening.

This study shows that the occurrence of polymorphic ventricular arrhythmias with predominant left bundle branch block morphology during isoproterenol testing is highly suggestive of ARVC in the absence of other structural heart disease. Polymorphic ventricular arrhythmias (PVCs and sustained and nonsustained VT) were observed in 90% of patients with ARVC. This is consistent with an earlier study showing polymorphic response to isoproterenol testing in 85% of patients with ARVC.

In contrast, a sustained monomorphic RVOT VT response during isoproterenol testing is a more benign condition because none of these patients developed ARVC during 6.4 years of follow-up.

Initially proposed in 1994, the diagnostic criteria for ARVC have recently been updated to improve their sensitivity. Demonstration of transmural fibrofatty replacement in the RV at autopsy or after surgery is usually reported as the gold standard for ARVC diagnosis. However, these findings are rarely available in clinical practice. Histological identification of fibrofatty replacement cannot be substituted by MRI identification because of MRI spatial resolution and the thin wall of the RV making difficult to characterize RV myocardium. The current revised TFC, although incorporating the latest imaging and genetic knowledge, cannot be considered as a gold standard and remains acknowledged as an imperfect indicator of the true presence of ARVC, particularly at its early stages.

In the present study, 6 of 41 patients with ARVC (14.6%) did not fulfill the diagnostic criteria for ARVC at initial evaluation but developed a patent form of ARVC a few years later. Importantly, arrhythmogenicity during isoproterenol testing was demonstrated in all of these patients (6/6) at the start of follow-up. The sensitivity and specificity of isoproterenol testing may have been underestimated during the first phase of the study because of the inadequacies in the revised TFC.
as a surrogate gold standard. The addition of the isoproterenol response to the current TFC would have allowed for an earlier identification of the disease as observed in 14.6% of the patient cohort. Kaplan–Meier analysis showed that the survival free from ARVC diagnosis was significantly lower in the positive isoproterenol testing group (exact log-rank test \( P<0.0001 \)), despite an initial negative diagnosis of ARVC, thereby demonstrating the potential usefulness of the test in the early stages of the disease. These patients should be followed up closely for prompt identification of ARVC. However, no patients with negative isoproterenol testing were diagnosed of having ARVC at the end of follow-up, indicating the further use of risk stratification to a lower risk group. Isoproterenol-induced ventricular arrhythmias at the early stages of the disease enhance the hypothesis that electric abnormalities seem to precede anatomic abnormalities.\(^{26}\)

Furthermore, patients who did not fulfill diagnostic criteria at the end of 5.6-year follow-up may develop patent ARVC with a longer follow-up period. Whether these results suggest the incremental role of isoproterenol testing to the current TFC warrant further investigation.

### Safety of Isoproterenol Testing

Our results showed that isoproterenol testing is safe. Only 14 of 412 tests (3.4%) were interrupted before the end of infusion because of VT induction. No syncope because of ventricular arrhythmias was observed, and no external electric cardioversion was required. However, despite the absence of any significant adverse events to date, we recommend that isoproterenol infusion should be performed with appropriate resuscitation equipment immediately accessible.

### Limitations

This is predominantly a retrospective study. However, patients were prospectively recruited from June 2010 to 2013, with the results validating the retrospective cohort. A low number of diagnosed patients with ARVC (\( n=41 \)) were included because of the inherently low prevalence of this disease. However, it comes from a series of >400 consecutive patients referred to a tertiary center for diagnostic evaluation for >10 years, and there patients with a prior established diagnosis of ARVC were not included (\( n=19 \)). The diagnosis of ARVC was made on the basis of the recent revised TFC\(^ {26} \) subject to an average follow-up of 5.6 years, which may still be an imperfect indicator of the true presence of ARVC.

The gold standard for diagnosis is demonstration of transmural fibrofatty replacement in the RV. Because biopsies have not been performed in any of the patients, we cannot be certain that ARVC diagnosed on the basis of TFC represent true patients with ARVC. However, the revised TFC, being the best available reference test, was used as a surrogate gold standard because of current limitations to diagnose ARVC. Consequently, sensitivity and specificity may be biased because of errors in the surrogate gold standard.\(^ {27} \)

Last, these prediction estimates were based on a 5.6-year follow-up duration, and patients were followed up for different durations. The estimated sensitivity and specificity levels may change with a longer follow-up period.

### Conclusions

Arrhythmogenicity during isoproterenol testing is highly sensitive (sensitivity, 91.4%); and negative predictive value, 99.1% particularly in the early stages of ARVC and can be safely performed in a controlled environment.

### Acknowledgments

We would like to thank Martine Bordage, Hélène Videau, Isabelle Brunello, Rozenn Mingam, and Valérie Aurillac for their assistance in data collection.

### Disclosures

None.

### References


**CLINICAL PERSPECTIVE**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty tissue replacement of the right ventricular myocardium. Ventricular arrhythmias can be the initial clinical manifestation and can lead to sudden cardiac death, especially in young people during adrenergic stimulation. Early detection is crucial but can be challenging because of the lack of specific diagnosis tools and incomplete penetrance of the disease. Morphological abnormalities may be absent particularly at the initial evaluation, in the early stages of the disease. Initially proposed in 1994, Task Force Criteria for diagnosis have been updated in 2010. We evaluated the diagnostic value of isoproterenol testing to diagnose early stage ARVC based on current Task Force Criteria. We shows that induction of polymorphic ventricular arrhythmias by isoproterenol is highly sensitive (sensitivity, 91.4%; and negative predictive value, 99.1%) in diagnosing ARVC and can be safely performed in a controlled environment. Important, arrhythmogenicity during isoproterenol testing was demonstrated in all 6 of 41 patients with ARVC who did not fulfill the diagnostic criteria for ARVC at initial evaluation but developed apparent ARVC a few years later, thereby demonstrating the potential usefulness of the test in detecting early disease. These patients should be followed up closely for prompt identification of ARVC. However, no patient with a negative isoproterenol test was diagnosed with ARVC by the end of follow-up, suggesting that this group can be spared further testing.
Diagnostic Value of Isoproterenol Testing in Arrhythmogenic Right Ventricular Cardiomyopathy

Arnaud Denis, Frédéric Sacher, Nicolas Derval, Han. S. Lim, Hubert Cochet, Ashok J. Shah, Matthew Daly, Xavier Pillois, Khaled Ramoul, Yuki Komatsu, Adlane Zemmoura, Sana Amraoui, Philippe Ritter, Sylvain Ploux, Pierre Bordachar, Mélèze Hocini, Pierre Jais and Michel Haïssaguerre

Circ Arrhythm Electrophysiol. 2014;7:590-597; originally published online June 26, 2014; doi: 10.1161/CIRCEP.113.001224

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/7/4/590

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org/subscriptions/