Diagnostic Value of Isoproterenol Testing in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Running title: Denis et al.; Isoproterenol testing in ARVC

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Abstract:

Background - Although the Task Force Criteria (TFC) for 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 arrhythmogenic right ventricular cardiomyopathy (ARVC).

Methods and Results - We evaluated 412 consecutive patients (213 men, age 41.5±16 years) referred for premature ventricular contractions (PVCs) evaluation or suspected ARVC. Isoproterenol testing was performed with continuous infusion of isoproterenol (45 μg/min) over 3 minutes. It was considered positive if there were either (1) polymorphic PVCs with at least one couplet or (2) sustained or non-sustained ventricular tachycardia (VT) with LBBB excluding right ventricular outflow tract VT. ARVC was diagnosed in 35 patients at initial evaluation (23 men, aged 42±15 years). Isoproterenol testing was positive in 32/35 (91.4%) ARVC patients and in 42/377 (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 6/6 (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.

Key words: arrhythmogenic right ventricular dysplasia cardiomyopathy, ventricular arrhythmia, diagnosis, isoproterenol
Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement of the right ventricular myocardium. Various estimates place the prevalence of this disease between 1 in 2,000 to 1 in 5,000. Mutations identified in ARVC patients are predominantly localized in genes encoding desmosomal proteins but may also affect the cardiac ryanodine receptor gene (RYR2) which gives rise to either ARVC type 2 or catecholaminergic polymorphic ventricular tachycardia (CPVT).

The clinical diagnosis of ARVC is often difficult in the early stage of the disease due to the lack of specific diagnostic tools and incomplete penetrance of the disease. 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. Indeed, cardiac magnetic resonance imaging (MRI) was considered normal or borderline in 14% and 26%, respectively, of patients newly identified with ARVC and 36% of ARVC patients with a history of sustained ventricular arrhythmias and/or cardiac arrest did not have major or minor criteria on cardiac imaging (MRI or echocardiogram). The diagnosis of ARVC is based on the 1994 Task Force Criteria (TFC), which were updated in 2010. While 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, as ARVC can result in sudden cardiac death (SCD), especially in young people during exertion. Endurance training provokes right ventricular arrhythmias in a murine model of reduced plakoglobin expression and adrenergic stimulation is well known to have a major role in induction of ventricular arrhythmias in ARVC. We hypothesized that isoproterenol, a commonly used nonselective beta-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 analysed retrospectively whereas patients were prospectively recruited from June 2010 to 2013. All patients underwent isoproterenol testing as 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 ventricular tachycardia (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 (SAECG), 2D transthoracic echocardiography, cardiac MRI, 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 ARVC patients. The diagnostic value of isoproterenol testing in ARVC was compared with diagnoses based on the revised TFC.\textsuperscript{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\textsuperscript{16} 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/or 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.

**Isoproterenol testing**

Isoproterenol testing was performed after withdrawal of β-blockers, calcium-channel blockers and other antiarrhythmic agents for at least 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 25mm/s and 10 mm/mV) was continuously recorded from the beginning of infusion up to 10 minutes after the cessation of infusion.

The test was considered positive if either (1) polymorphic (≥ 3 morphologies) PVCs and at least one couplet or (2) sustained or non-sustained monomorphic or polymorphic VT with left bundle branch block (LBBB) 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 over 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 at least 30 seconds. Non-sustained VT was defined as a
ventricular rhythm faster than 120 bpm lasting for at least 3 beats that spontaneously resolves in less than 30 seconds. Polymorphic PVCs were defined as PVCs with 3 or more different morphologies. A vasovagal response was defined as occurrence of an accelerated idioventricular rhythm (ectopic ventricular rhythm with at least 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 ± standard deviation 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’s χ² test. Where the expected value was <5, the Fisher’s exact test was used instead. The sensitivity and specificity of isoproterenol testing was 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.²³ A value of p<0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, Ill) and StatXact version 10 (Cambridge, MA, USA).

**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 ARVC patients, and 152 ± 19 bpm in non ARVC patients, 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 ARVC patients prompting termination of the test before reaching maximal sinus rhythm heart rate.

Isoproterenol testing was positive in 74/412 (18%) patients. It was positive in 32/35 (91.4%) patients in whom the diagnosis of ARVC was established and in 42/377 (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 ARVC patients consisted of: (1) polymorphic PVCs and at least one couplet, 5/35 (14.3%) vs. 22/377 (5.8%) in patients without ARVC (p = 0.05); (2) monomorphic non sustained VT, non RVOT morphology, 1/35 (2.9%) vs. 1/377 (0.3%) in patients without ARVC; (3) polymorphic non-sustained VT, 17/35 (48.6%) vs. 13/377 (3.4%) in patients without ARVC (p < 0.0001); and (4) sustained polymorphic VT, 9/35 (25.7%) vs. 6/377 (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 16 at inclusion. Sensitivity, specificity, positive and negative predictive values of isoproterenol testing to diagnose ARVC were 91.4% ([CI 95%] 90.5-100), 88.9% ([CI 95%] 85.7-92), 43.2% and 99.1% respectively (Table 3).
Monomorphic sustained or non-sustained RVOT VT (without any other ventricular arrhythmias) were observed in 0/35 (0%) ARVC patients vs. 27/377 (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 ARVC patients.

Sixteen tests (3.9%) were interrupted before the end of 3 minutes due to VT induction. No syncope was observed and β-blocker injection restored sinus rhythm without need for electrical 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 suffered 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. 30/41 (73.2%) of ARVC patients had genetic screening for ARVC mutations, in whom 10 patients had a mutation identified (9 Plakophilin-2 and 1 Desmocolin-2). 24/371 (6.5%) of non-ARVC patients had genetic screening and no patient had a mutation.
Isoproterenol testing in ARVC patients not recognized at initial evaluation

The isoproterenol test performed at study inclusion was positive (1 polymorphic sustained VT, 3 polymorphic non-sustained VT and 2 polymorphic PVCs with couplets) in all 6 patients that did not fulfil 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 years 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 performed up to 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 non-ARVC patients with positive isoproterenol testing

Thirty-six patients that had a positive isoproterenol test were not diagnosed of having ARVC according to the revised TFC at the end of follow-up. Out of these patients, at mean follow-up of 5.7±5.1 years, 6 patients clinically “suspected” of having ARVC did not fulfil 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 CPVT, and no definite diagnosis could be made in 23 patients (17/23 had polymorphic PVCs with at least one 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 non-controlled study\textsuperscript{24} 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 LBBB morphology during isoproterenol testing is highly suggestive of ARVC in the absence of other structural heart disease. Polymorphic ventricular arrhythmias (PVCs, sustained and non sustained VT) were observed in 90% of ARVC patients. This is consistent with an earlier study showing polymorphic response to isoproterenol testing in 85% of ARVC patients.\textsuperscript{25}

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

Initially proposed in 1994\textsuperscript{15}, the diagnostic criteria for ARVC have recently been updated to improve their sensitivity.\textsuperscript{16} 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, can not be considered as
a gold standard and remains acknowledged as an imperfect indicator of the true presence of ARVC, particularly at its early stages.\textsuperscript{16}

In the present study, 6 of 41 ARVC patients (14.6\%) did not fulfil 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 due to 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. On the other hand, no patients with negative isoproterenol testing were diagnosed of having ARVC at the end of follow-up, indicating the further utility of risk stratification to a lower risk group. Isoproterenol-induced ventricular arrhythmias at the early stages of the disease enhance the hypothesis that electrical abnormalities appear to precede anatomical abnormalities.\textsuperscript{26} Furthermore, patients who did not fulfil diagnostic criteria at the end of 5.6 years 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.

\textbf{Safety of isoproterenol testing}

Our results showed that isoproterenol testing is safe. Only 14/412 tests (3.4\%) were interrupted
before the end of infusion due to VT induction. No syncope due to ventricular arrhythmias was observed and no external electrical 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 ARVC patients (n=41) were included because of the inherently low prevalence of this disease. However, it comes from a series of more than 400 consecutive patients referred to a tertiary center for diagnostic evaluation over >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 TFC16 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 right ventricle. 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 due to current limitations to diagnose ARVC. Consequently, sensitivity and specificity may be biased due to errors in the surrogate gold standard.27

Lastly, these prediction estimates were based upon a 5.6 years 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.
Conclusion

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.

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

Conflict of Interest Disclosures: None.

References:


**Table 1**: Clinical characteristics of the study population at inclusion

<table>
<thead>
<tr>
<th></th>
<th>ARVC n=35</th>
<th>No ARVC n=377</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>Number 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>Number 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARVC</td>
<td>8 (22.9)</td>
<td>11 (2.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SCD</td>
<td>3 (8.6)</td>
<td>27 (7.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Initial symptoms†, n (%)</td>
<td></td>
<td></td>
<td></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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphic PVC</td>
<td>11 (32.4)</td>
<td>282 (74.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polymorphic PVC</td>
<td>15 (44.1)</td>
<td>24 (6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-sustained 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: arrhythmogenic right ventricular cardiomyopathy; SCD: sudden cardiac death; PVC: premature ventricular contraction; VT: ventricular tachycardia

* Pearson’s chi-square test or Fisher’s exact test (if n<5) were used for categorical variables and Student t test was used for continuous variables.

† One subject could be included in several items.
Table 2: Results of isoproterenol testing based on the revised TFC at inclusion.

<table>
<thead>
<tr>
<th></th>
<th>ARVC n=35 (%)</th>
<th>No ARVC n=377 (%)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive isoproterenol</td>
<td>32 (91.4)</td>
<td>42 (11.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>testing†, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphic PVC and</td>
<td>5 (14.3)</td>
<td>22 (5.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>couplet(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphic non-sustained 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 non-sustained 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphic non-sustained VT, RVOT morphology</td>
<td>0 (0)</td>
<td>16 (4.3)</td>
<td>0.2</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: arrhythmogenic right ventricular cardiomyopathy; bpm: beats per minute; PVC: premature ventricular contraction; RVOT: right ventricular outflow tract; VT: ventricular tachycardia

* Pearson’s chi-square test or Fisher’s exact test (if n<5) were 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.

Table 3: Diagnostic performance of isoproterenol testing based on the revised TFC at inclusion.

<table>
<thead>
<tr>
<th></th>
<th>ARVC n=35 (%)</th>
<th>No ARVC n=377 (%)</th>
<th>Positive predictive value=43.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive isoproterenol</td>
<td>32 (91.4)</td>
<td>42 (11.1)</td>
<td></td>
</tr>
<tr>
<td>testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative isoproterenol</td>
<td>3 (8.6)</td>
<td>335 (88.9)</td>
<td>Negative predictive value=99.1%</td>
</tr>
<tr>
<td>testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity=91.4%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Specificity=88.9%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n=412 (100)</td>
<td></td>
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</table>

ARVC: arrhythmogenic right ventricular cardiomyopathy
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis</th>
<th>Initial evaluation</th>
<th>Follow-up</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Male, 30 years old</td>
<td>Polymorphic PVCs with at least one couplet</td>
<td>Minor criteria: - Sustained VT of LBB morphology with unknown axis - Inverted T wave in leads V1 and V2 in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
<td><strong>Major criteria</strong> - Sustained VT of LBB morphology with superior axis - Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB) - By MRI, regional RV dyskinesia, ratio of RV end-diastolic volume to BSA ≥110 mL/m² and RV ejection fraction ≤40% - Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Female, 19 years old</td>
<td>Polymorphic non sustained VT</td>
<td>Minor criteria: - &gt; 500 ventricular extrasystoles per 24 hours (Holter)</td>
<td><strong>Major criteria</strong> Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Male, 41 years old</td>
<td>Polymorphic non sustained VT</td>
<td>Minor criteria: - Sustained VT of LBB morphology with unknown axis - Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG</td>
<td><strong>Major criteria</strong> - By MRI, regional RV dyskinesia and RV ejection fraction ≤40% - Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Male, 19 years old</td>
<td>Polymorphic non sustained VT</td>
<td>Minor criteria: - &gt; 500 ventricular extrasystoles per 24 hours (Holter)</td>
<td><strong>Major criteria</strong> - By MRI, regional RV dyskinesia and RV ejection fraction ≤40% - Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Male, 43 years old</td>
<td>Polymorphic sustained VT</td>
<td>Minor criteria: - &gt; 500 ventricular extrasystoles per 24 hours (Holter) - Late potential by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG - Terminal activation duration of QRS ≥55ms measured from the nadir of the S wave to the end of the QRS, including R’, in V1, V2 or V3, in the absence of complete right bundle-branch block</td>
<td><strong>Major criteria</strong> - By MRI, regional RV dyskinesia and RV ejection fraction ≤40% - Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Male, 14 years old</td>
<td>Polymorphic PVCs with at least one couplet</td>
<td>Minor criteria: - Familial history (clinical diagnosis based on present criteria)</td>
<td><strong>Major criteria</strong> - Inverted T wave in the right precordial leads (V1, V2 and V3) or beyond in individuals &gt; 14 years of age (in the absence of complete RBBB)</td>
</tr>
</tbody>
</table>

**Table 4:** Characteristics of patients (n=6) with positive initial isoproterenol testing not fulfilling TFC but subsequently developing a patent form of ARVC

ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia, BSA: body surface area, ICD: implantable cardioverter defibrillator, LBB: left bundle branch, LBBB: left bundle branch block, MRI: magnetic resonance imaging, RBBB: right bundle branch block, RV: right ventricle, RVOT: right ventricular outflow track, SAECG: signal-averaged electrocardiography, TFC: task force criteria, VT: ventricular tachycardia
Figure Legends:

**Figure 1:** Negative isoproterenol testing. - Heart rate increases quickly to the maximum between the first and the second minute. The maximal average heart rate was 151 ± 19 bpm, 85 ± 11% of the age-adjusted maximum heart rate. A: Before isoproterenol testing; B: 1 minute after the start of isoproterenol infusion; C: 2 minutes after the start of isoproterenol infusion; D: End of isoproterenol infusion.

**Figure 2:** Positive isoproterenol testing in 8 ARVC patients. – Polymorphic ventricular arrhythmias (sustained and non sustained VT with left bundle branch block morphology predominance) induced during isoproterenol testing in 8 ARVC patients. A: 45 year-old woman; B: 33 year-old man; C: 25 year-old woman; D: 26 year-old woman; E: 19 year-old man; F: 26 year-old man; G: 46 year-old man; H: 43 year-old man.

**Figure 3:** Kaplan-Meier curve of ARVC diagnosis depending on isoproterenol testing results.
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