A arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an important cause of sudden death in young adults. Since Marcus and Fontaine’s initial report of a series of 24 patients with this condition in 1982 remarkable progress has been made in the understanding of all aspects of this disease. These advancements include improved understanding of (1) the natural history of ARVD/C, (2) optimal approaches for diagnosis, (3) the genetic basis of this condition, (4) the fundamental pathophysiologic mechanisms of ARVD/C, (5) the link between ARVD and exercise, and (6) sudden death prevention. Although far more work remains, the degree of scientific progress is remarkable.

In the present issue of Circulation: Arrhythmia and Electrophysiology, Denis et al. report the results of their investigation into the role of high-dose isoproterenol infusions in the diagnosis of ARVD/C. A total of 412 consecutive patients (52% men; 42±16 years) referred for evaluation of premature ventricular contractions (PVCs) or ARVD/C during a 13-year period of time was included in this report.

Subjects in the first 10 years of this study were analyzed retrospectively, whereas subjects enrolled between 2010 and 2013 were prospectively included in this analysis and followed up to determine whether they met criteria for ARVD/C over time. Thirty five of these patients had been diagnosed with ARVD/C based on the revised 2010 Task Force Criteria (TFC) at the time of their initial evaluation. The isoproterenol infusion consisted of intravenous administration of high-dose (45 μg/min) isoproterenol for 3 minutes. A continuous ECG was recorded during and for ≤10 minutes after the infusion.

The test was interpreted as being positive if polymorphic PVCs (>3 morphologies) and ≥1 couplet were observed or if sustained or nonsustained monomorphic, polymorphic, or polyventricular tachycardia (VT) with predominantly left bundle branch block morphology not typical for right ventricular outflow tract (RVOT) VT was observed. The isoproterenol test was positive in 74 of 412 (18%) patients. The test was positive in 32 of 35 (91.4%) patients with an established ARVD/C diagnosis and in 42 of 377 (11.1%) patients without ARVD/C. A vasovagal response was observed in 33 (8%) of tests. The resultant sensitivity, specificity, positive, and negative predictive values of isoproterenol testing to identify patients diagnosed with ARVD/C based on the 2010 TFC were 91.4%, 88.9%, 43.2%, and 99.1%, respectively. Monomorphic sustained or nonsustained RVOT VT were observed in 0 of 35 patients with ARVD/C versus 27 of 377 (7.2%) of patients without ARVD/C. During a median follow-up of 5 years, 6 of the initial non-ARVD/C group met diagnostic criteria for ARVD/C. Each of these individuals had a positive isoproterenol response. None of the patients who had typical RVOT VT developed ARVD/C during follow-up. On the basis of these data, we determined that survival free from a diagnosis of ARVD/C was lower in the negative isoproterenol group versus the positive isoproterenol response group. Genetic screening was performed in 30 of the 41 patients eventually diagnosed with ARVD/C (with a pathogenic mutation identified in 10) and in 24 of 371 non-ARVD/C patients.

At first read, one may quickly conclude that we now have a new and improved method by which to diagnose ARVD/C. And that the time has come to encourage all centers that evaluate patients for ARVD/C to develop the infrastructure needed to administer high-dose isoproterenol infusions safely. Whether this requires that the patient to be in an electrophysiology laboratory, or a monitored floor, or in an outpatient clinic remains somewhat unclear. But after rereading the article and further reflection, we conclude that we are not there yet. This article reports provocative but preliminary findings.

We have learned a lot about how to diagnose ARVD/C during the past 30 years. The Task Force Criteria developed in 1994 provided a specific set of criteria to diagnose ARVD/C. This set the stage for the break through discoveries of the genetic basis of ARVD. Over time it became clear that the initial diagnostic criteria for ARVD/C, while highly specific, lacked sensitivity and were also difficult to apply as many of the criteria were not quantitative. This led to the revised 2010 TFC. These revised 2010 TFC have been well accepted by clinicians and researchers alike.

Let us now look with a discerning and critical eye at the article by Denis et al. Interpreting the results of this study in the context of clinical application is challenging because the “devil is in the details” and detailed information is not provided. An
initial question that we concern is exactly what population of patients were enrolled in this study. Although the Methods section states that “all patients … referred for evaluation of PVCs or suspicion of ARVD/C were enrolled, we remain perplexed.” A review of the summary data tells us that 3 patients had aborted sudden death and 45 had syncope. Clearly, these patients are not routine patients referred for the evaluation of asymptomatic PVCs. We must conclude that the patients enrolled in this study were highly heterogeneous, and only selected patients were referred to a tertiary hospital for a variety of reasons and with a variety of suspected conditions. Although we are not certain, it seems that each of these patients had a sufficiently concerning reason to justify an inpatient hospitalization and evaluation. Although the study states that each patient underwent complete testing, including a cardiac MRI, the results of these detailed evaluations and detailed clinical information on a patient-by-patient basis are not provided. At the least, we would have hoped to have seen detailed phenotypic information on each of the 35 patients initially diagnosed with ARVD/C, as well as the 6 patients diagnosed with ARVD/C on follow-up. In our experience, the mean age of presentation of ARVD/C is in the early 30s. Genetic testing of well-phenotyped probands identifies a pathogenic mutation in 60%. In this context, it seems surprising that the mean age of patients with ARVD/C in this series is in the early 40s, at that a pathogenic mutation was only observed in a third of patients diagnosed with ARVD/C. Table 4 provides some patient-specific information about the 6 patients who developed ARVD/C over time, but many important details are missing. Ideally, the authors would have provided the results of initial screening of these patients at entry into the study based on the 2010 TFC, and then would have provided the detailed results of their repeat screening that led to the diagnosis years later. One of the features of the 2010 TFC is that a point system can be used: 2 points for each major criteria and 1 point for each minor criteria. Using this system, patients can be phenotyped as having definite ARVD/C (≥4 points), probably ARVD/C (3 points), or are unlikely to have ARVD/C≤2 points. Using this approach, it seems that most of the patients subsequently diagnosed with ARVD/C, and detected early by the isoproterenol infusion protocol, would have been initially classified as having probable ARVD/C and followed up closely. At the end of the day, it remains unconvincing whether the isoproterenol infusion test adds significantly to the 2010 TFC when it comes to the diagnosis of ARVD/C.

The concept of using a high-dose isoproterenol test as a screening/diagnostic test for ARVD/C is novel and potentially of great importance. It is worth noting, in this regard, that based on the authors’ initial report on the role of an isoproterenol infusion in patients with ARVD/C many years ago, we have been applying this technique in patients with ARVD/C brought to the electrophysiology laboratory for VT ablation. Consistent with the results of the study by Denis et al, we have also found that a high-dose isoproterenol infusion consistently induced polymorphic PVCs and sustained VT in patients with ARVD/C. We have also extended the use of high-dose isoproterenol infusion as a method to identify patients with ARVD/C who are at risk for developing arrhythmias. In our opinion, given the risk of arrhythmia induction and hypotension observed with high-dose isoproterenol, this method may best be reserved for a controlled setting, such as the electrophysiology laboratory.

Like many excellent articles, this study raises far more questions than it answers. First, what is the additive value of an isoproterenol infusion to diagnosis of ARVD/C based on the 2010 TFC? Second, how effectively can this protocol distinguishes ARVD/C from idiopathic RVOT VT? Third, can this test be used to risk stratify patients with ARVD/C for sudden death risk and to determine who needs an implantable cardioverter-defibrillator? And fourth, what is the role of an isoproterenol infusion as an end point to assess the efficacy of antiarrhythmic drug therapy or catheter ablation. Finally, we are grateful to Denis et al for the considerable effort expended to collect, analyze, and publish this excellent article.

Disclosures
Dr Calkins has received research support from Medtronic and St Jude Medical. Dr Tandri reports no conflicts.

References

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High-Dose Isoproterenol Testing for Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Is There a Role?
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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An erratum has been published regarding this article. Please see the attached page for:
/content/8/1/248.full.pdf
In the article “High-Dose Isoproterenol Testing for Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Is There a Role?” by Calkins and Tandri, which was published in the August 2014 issue (Circ Arrhythm Electrophysiol. 2014;7:565–566), a correction was needed.

Two numbers were erroneously indicated as representing years and not ages. The sentences have been corrected as follows: “In our experience, the mean age of presentation of ARVD/C is in the early 30s. Genetic testing of well-phenotyped probands identifies a pathogenic mutation in 60%. In this context, it seems surprising that the mean age of patients with ARVD/C in this series is in the early 40s, at that a pathogenic mutation was only observed in a third of patients diagnosed with ARVD/C.”

The compositor apologizes for the error.

The online version of the article has been corrected.