JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 68, NO. 23, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.04.072

EDITORIAL COMMENT

Further Progress in Predicting Life-Threatening Arrhythmias in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy*

Cynthia A. James, PhD, Hugh Calkins, MD

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an important cause of sudden cardiac death (SCD) in young adults. Since ARVC was first described in the modern scientific published data in 1982 in the seminal work of Marcus et al. (1), remarkable progress has been made. Notable advancements include: 1) the discovery of the genetic basis of the disease; 2) optimal approaches for diagnosis; 3) definition of the natural history of ARVC; 4) greater understanding of fundamental pathophysiologic mechanisms; 5) defining the critical link between exercise and the development and outcomes of ARVC; 6) identification of risk factors for malignant ventricular arrhythmias; and 7) increased recognition of the role of implantable cardioverter-defibrillators (ICDs) and catheter ablation in management (2).

SEE PAGE 2540

In this issue of the *Journal*, Mazzanti et al. (3) report the natural history and arrhythmic outcomes of 301 patients with ARVC from Pavia, Italy. With publication of this paper, the body of knowledge regarding risk prediction and management strategies advances 1 step further. The patient population included 163 probands and 138 family members who met 2010 diagnostic criteria. Overall, 73 patients (24%) experienced at least 1 life-threatening arrhythmic event (LAE), defined as SCD, aborted cardiac arrest, or an electrical storm. The first LAE resulted in SCD in 26 patients, resuscitation in 15, and survival in 32 who had an ICD in place. A total of 47 (18%) patients experienced a first LAE during a median 5.8 years of follow-up. The cumulative probability of a first LAE during follow-up was 14% at 5 years, 23% at 10 years, and 30% at 15 years. History of syncope, hemodynamically tolerated monomorphic ventricular tachycardia (VT), atrial fibrillation, strenuous exercise, and male sex were independent predictors of LAE in follow-up.

The authors presented sobering data on the efficacy of antiarrhythmic medication and catheter ablation in preventing life-threatening arrhythmias. Among the 278 patients in whom follow-up was available, 119 (43%) were treated with a beta-blocker, sotalol, or amiodarone. The rate of LAE in these patients did not differ before and after initiation of this therapy. Likewise, catheter ablation (performed in 27 patients) did not decrease the rate of LAE and VT that occurred within the 2 years of ablation in 59% of those patients. ICDs were implanted in 81 (29%) patients, of whom 31 had an LAE successfully terminated by their device during follow-up. One patient with an ICD died due to VT storm. It is notable that most patients receiving ICD therapy for an LAE were being treated with antiarrhythmics (sotalol in 9 patients, amiodarone in 5 patients, and a beta-blocker in 12 patients), and 7 patients had undergone catheter ablation.

This study is a welcome addition to the published data as we continue our quest to fully understand all aspects of ARVC. This study is unique for a number reasons. First, it represents the initial description of clinical characteristics of patients with ARVC from a highly respected Italian center. Second, this paper

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Medicine, Division of Cardiology, Johns Hopkins University, Baltimore, Maryland. Dr. James receives salary support from St. Jude Medical Foundation and Boston Scientific. Dr. Calkins is a consultant for Medtronic and St. Jude Medical; and receives research support from the St. Jude Medical Foundation and Boston Scientific.

presents a comprehensive analysis of outcomes of this patient population. Third, this study uses a unique approach to defining outcomes focusing on life-threatening arrhythmic events. And finally, this study attempts to address the important question of whether therapies other than ICDs improve arrhythmic outcomes of ARVD/C patients.

We would like to focus our comments initially on what we believe are the most important findings of this study. First, this study identified hemodynamically stable monomorphic VT as an independent risk factor for an LAE among patients with ARVC. This finding, consistent with our own experience, has important implications in patient management. Some investigators in the field have argued for decades that patients with hemodynamically stable VT have an excellent prognosis and that ICD implantation is not warranted. Reflecting this belief are the recommendations of the recent consensus document on ARVC management, which lists a history of sustained VT as a Class IIA indication for ICD implantation (4). In the United States, the standard of care has always been to implant an ICD in these individuals. Perhaps reflecting this difference in approach, the proportion of individuals presenting alive who died of a lethal arrhythmia in follow-up in this study (12 of 278; 4.3%) is nearly double what we recently observed in a cohort of Dutch and U.S. patients with ARVC (16 of 646; 2.5%) (5). In the U.S./Dutch cohort, ICDs were implanted in 440 of 598 patients with ARVC presenting alive, and lethal arrhythmias occurred in only 2 (0.45%) ICD-treated individuals.

A second important finding was the identification of exercise as an important risk factor for an LAE. This observation added to the chorus of studies from throughout the world calling attention to the fact that patients with ARVC who participate in competitive exercise have worse outcomes (6–8). Finally, the results of this study provided additional support to the long-held belief that pharmacological agents and catheter ablation do not lower the risk of sudden death in ARVC, but rather should be used to reduce the frequency of symptomatic VT events and, in doing so, improve quality of life (9). We advise beta-blockers for patients with ARVC because beta-blockers have been shown to reduce SCD and help reduce inappropriate ICD therapies in other patient populations, and likely reduce VT events in patients with ARVC. Most VT events in patients with ARVC occur during exercise when catecholamine levels are high. It is also worthwhile to consider the recent report that high-level catecholamine infusions invariably triggered sustained ventricular arrhythmias in patients with ARVC (10).

Although we have summarized and highlighted the important findings of this paper, we would be remiss in our duties as editorialists to fail to point out some of the study's limitations and omissions. One of the most notable limitation relates to the definitions employed. The authors have come up with a novel study endpoint that they term "life-threatening arrhythmic event," defined as SCD, aborted cardiac arrest, or electrical storm. The conventional definition of VT storm is 3 or more separate episodes of sustained ventricular tachycardia or fibrillation within 24 h. The authors of this study, for unknown reasons, defined electrical storm as 3 or more separate episodes of ventricular fibrillation or hemodynamically not tolerated (syncopal) VT within 24 h requiring resuscitation and/or defibrillation. We do not believe it is helpful to the field to develop these types of novel definitions as it is important to have a common language to compare study outcomes. Prior studies, including those conducted by our program, have used the endpoints of sustained ventricular arrhythmia or a potentially lethal ventricular arrhythmia, defined as a sustained ventricular arrhythmia with a cycle length of ≤240 ms (11). Another small detail, which we find novel, was the very strict definition of "asymptomatic" that Mazzanti et al. (3) used in this study. Asymptomatic was defined as no history of sustained VT, LAE, or arrhythmic syncope. This contrasted with our approach to defining symptoms, which is much broader and includes palpitations, pre-syncope, and dyspnea attributed to ARVC. We suspect this strict definition may explain their finding that more than one-half of LAEs occurred prior to onset of symptoms.

There were several other limitations of this study. First, a close look at the methods and results sections reveals that patients were incompletely phenotyped and represented a group with relatively limited structural disease. It is striking to us that an electrocardiogram, which all would agree is the single most important test for diagnosing ARVC, was only obtained in 85% of patients. We were surprised to learn they had diagnosed ARVC in a child 1.9 years of age. In our 17-year experience with ARVC, we have never diagnosed ARVC at an age <10 years. The low yield of genetic testing also differed from our experience. A pathogenic mutation was identified in only 37% of patients with ARVC (46 of 163; 28% of families) in this study. This low yield of genetic testing can be explained to some degree by the fact that comprehensive genetic testing was not consistently performed in the study's subjects. This contrasted with our recent series involving 1,001 patients and family members in which a pathogenic mutation was identified in nearly 70% of individuals (63% of probands). Taken together, these

issues lead us to be concerned regarding the care taken to properly phenotype patients in this study.

Another limitation was that several variables associated with likelihood and timing of arrhythmias in predicting arrhythmic outcomes in other studies were not included. Structural heart disease, particularly as visualized by cardiac magnetic resonance, has been found to be a strong predictor of arrhythmic events (12) but was not included in this model. Likewise, the influence of genotype was considered as a modifier of neither the likelihood nor the timing of a first LAE. We recently found that patients with ARVC with desmosomal mutations had earlier disease onset than those without (5). Our studies have also found that proband status is of great importance in predicting outcome with family members who are at markedly lower risk, and because of this critical effect of proband status, we believe it is preferable to present the outcomes of probands separately from the outcomes of family members (5). Although not emphasized in the paper, it is important to note that this study confirmed that family members are at considerably lower risk.

Finally, although we commend the study team for carefully accounting for survivorship bias and excluding patients from their risk set between birth and diagnosis, we would like to point out that it is possible to include the period prior to enrollment in natural history and penetrance studies when a pedigree-based approach to ascertainment is used. If mutation status of an individual is known or can be calculated on the basis of position in the pedigree, and hard endpoints are used (e.g., sudden cardiac death), each at-risk individual in a family can be included, as the key risk factor (a mutation) is present from birth. Indeed, by excluding individuals prior to diagnosis, phenotypic severity may be underestimated, as the relatively large proportion of fatal arrhythmic events occurring as the first ARVC presentation are not included.

At the end of the day, we want to congratulate the authors for the considerable effort expended in assembling this impressive cohort of subjects and presenting a comprehensive report on the clinical characteristics and outcomes of these patients. The message that should resonate from this and other studies is that ARVC is a highly malignant disease. The 2 most important components of treatment are ICD implantation in high-risk individuals and exercise restriction. Although pharmacological therapy and catheter ablation reduce the frequency of VT events and ICD therapies, they should not be relied on to reduce the risk of sudden death.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Hugh Calkins, Division of Cardiology, Johns Hopkins Hospital, Sheikh Zayed Tower-7125R, 1800 Orleans Street, Baltimore, Maryland 21287-6568. E-mail: hcalkins@jhmi.edu.

REFERENCES

1. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384–98.

2. Calkins H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy—three decades of progress. Circ J 2015;79:901–13.

3. Mazzanti A, Ng K, Faragli A, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. J Am Coll Cardiol 2016;68:2540–50.

4. Corrado D, Wichter T, Link MS, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an International Task Force Consensus Statement. Circulation 2015;132:441–53.

5. Groeneweg JA, Bhonsale A, James CA, et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. Circ Cardiovasc Genet 2015;8:437–46.

6. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.

7. Sawant AC, Te Riele AS, Tichnell C, et al. Safety of American Heart Association minimum recommended exercise for desmosomal mutation carriers. Heart Rhythm 2016;13:199–207.

8. Saberniak J, Hasselberg NE, Borgquist R, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. Eur J Heart Fail 2014;16:1337–44.

9. Philips B, te Riele AS, Sawant A, et al. Outcomes and ventricular tachycardia recurrence characteristics after epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Heart Rhythm 2015;12:716–25.

10. Denis A, Sacher F, Derval N, et al. Diagnostic value of isoproterenol testing in arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 2014;7:590–7.

11. Bhonsale A, James CA, Tichnell C, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. J Am Coll Cardiol 2011;58:1485–96.

12. te Riele AS, Bhonsale A, James CA, et al. Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1761–9.

KEY WORDS implantable cardioverter-defibrillator, proband, sudden cardiac death, ventricular tachycardia