JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 5, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.09.006

EDITORIAL COMMENT

Moving From Multimodality Diagnostic Tests Toward Multimodality Risk Stratification in ARVC*

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is probably, within the field of cardiology, the single most complex disease to diagnose. It is required that we follow the recommendations stated in the 2010 Task Force criteria (TFC), obtaining points on structural, histological, electrocardiographic, arrhythmic, and genetic features of the diseases (1). Even when we know the patient carries a disease-causing mutation, he/she might have definite, possible, or borderline ARVC depending on how many abnormalities have been identified. Indeed, this disease is notorious for its reduced penetrance and variable disease expressivity, even within families carrying an identical pathogenic mutation in a desmosomal gene (2,3). ARVC is known to be associated with potential life-threatening arrhythmias, and this remains a major concern for both cardiologists and the individual patient (4). Nevertheless, it has been shown that the outcome is favorable after diagnostic criteria are met and treatment according to guidelines is initiated (4). Reported mortality rates vary between 0.08% and 3.6%/year after the diagnosis has been made (excluding sudden cardiac death victims) (5). In the past decades, major advances have been made in defining the genetic basis of ARVC (3,6). These advances have helped to identify a large group of family members who share the same genetic background and are therefore at risk for adverse arrhythmic outcome. Identifying predictors for ventricular arrhythmias during the early ARVC stages has been a focus for research (7–10). It seems that the presence of both electrical and structural abnormalities, as defined by the 2010 TFC, provides sufficient prognostic value in this group (8). However, because our methods for detecting pathology, particularly in the field of cardiac imaging, are improving, we are confronted by subtle phenotypic expressions of this disease in early ARVC that are currently of unknown significance (9,11). The clinical challenge in caring for the individual patient now primarily lies in the early ARVC stages without overt phenotypic expression, and the question remains: which individuals benefit the most from life-style modifications, treatment with antiarrhythmic medications, and implantable cardioverter-defibrillators? The ultimate goal for practicing cardiologists is to provide a specific, tailored approach to each patient with ARVC, such as exists in patients with HCM (12). This would guide our efforts toward those patients who would benefit most while safely implementing a "watchful waiting" strategy in low-risk patients. New cardiac imaging techniques that identify subtle pathology could be of incremental value in the clinical challenge of developing tailor-made strategies during early ARVC.

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In this issue of *iJACC*, Leren et al. (13) investigated this clinically relevant problem using a multimodality approach. In this study, they aimed to establish the incremental value of a parameter called mechanical dispersion, assessed by echocardiographic deformation imaging, which is a functional representation of disease expression. Sarvari et al. (10) have previously shown that this parameter is related to ventricular arrhythmias in patients with ARVC.

Leren et al. (13) included a total of 162 individuals: 89 patients who met the ARVC diagnosis (classified as "overt AVRC") and 73 individuals with "early ARVC" (predominantly family members of patients with ARVC with confirmed pathogenic mutations that did

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

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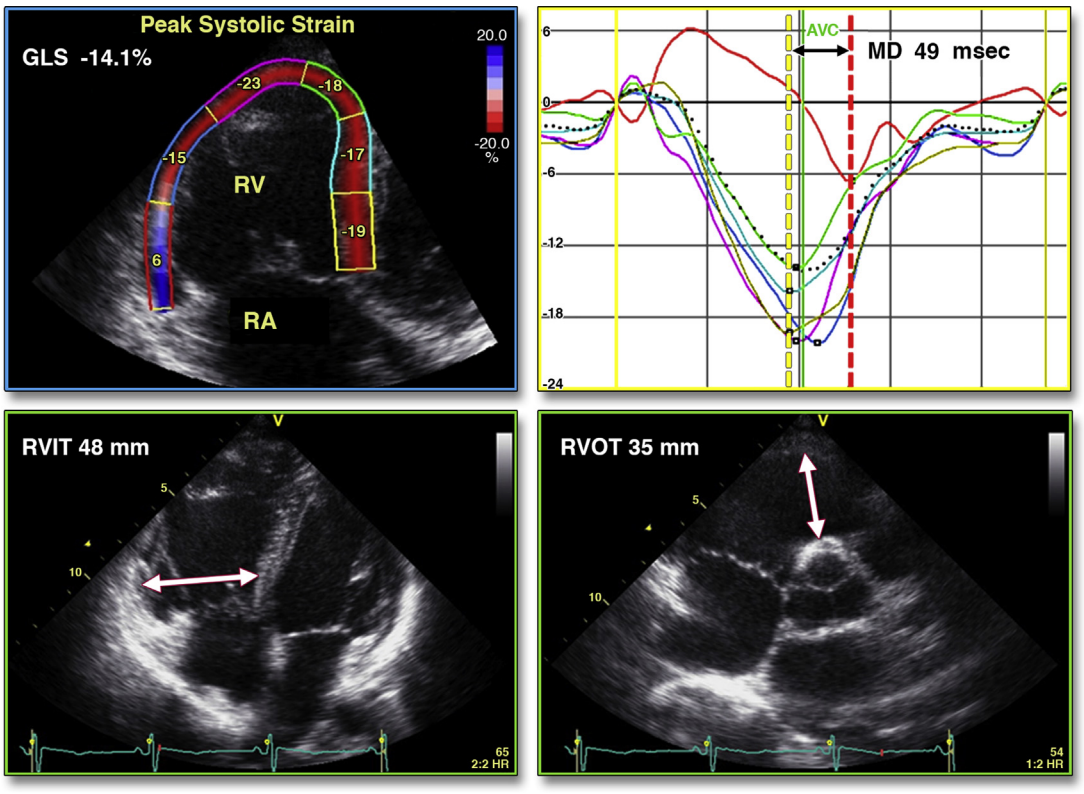
FIGURE 1 **Proposed Echocardiographic Measurements During Follow-Up**

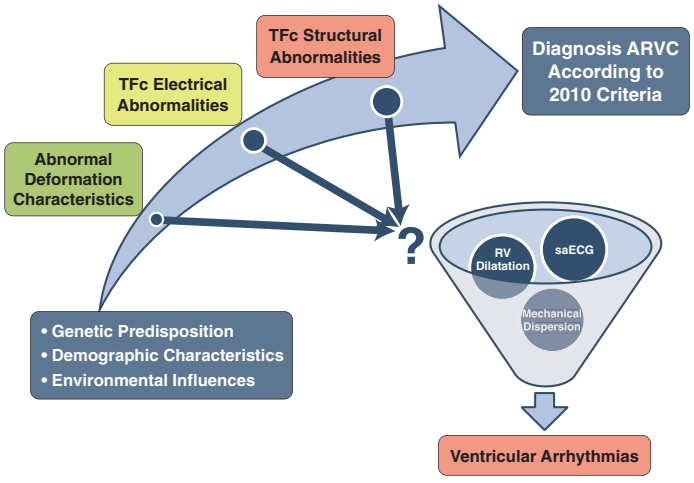


Proposed parameters on echocardiography by Leren et al. (13) to evaluate the risk of AE during follow-up in a patient with arrhythmogenic right ventricular cardiomyopathy at our institution. **(Top left)** The reduced global longitudinal stain (GLS). **(Top right)** The prolonged mechanical dispersion (MD) of ≥37 ms. **(Bottom)** The dilation of the RVIT ≥40 mm and RVOT ≥34 mm. AVC = aortic valve closure; RA = right atrium; RV = right ventricle; RVIT = right ventricular inflow tract; RVOT = right ventricular outflow tract.

not fulfill the ARVC diagnosis). The cross-sectional study was performed in a single center (13). Arrhythmic events (AE) were obtained retrospectively at inclusion, and were defined as documented non-sustained or sustained ventricular tachycardia, syncope, or aborted cardiac arrest. Finally, the authors aimed to identify markers of ARVC disease on the electrocardiogram (ECG) (as stated in the TFC) and echocardiography (right ventricular [RV] dimensions, right-left ventricular function, and deformation parameters including mechanical dispersion), which showed an association with previous arrhythmic events. In the period prior to inclusion, AE occurred in over 50% of subjects. This was largely driven by the patients with overt AVRC, but nevertheless, AE also occurred in 21% of patients with early ARVC. In the patients with overt ARVC, almost all investigated parameters on imaging and ECG were significantly more abnormal in the AE group compared with those without AE. This substantiates the hypothesis that the more affected the heart, the higher the likelihood of AE. In the smaller cohort of patients with early ARVC, the event rate was lower and the AE were less severe. Only RV diameter, RV mechanical dispersion, and abnormalities on the signal averaged ECG were associated with AE in the past. When combining these parameters, the association became even stronger (**Figure 1**).

Although this study provides us with very specific cut-off values and recommendations for clinical decision making, we would like to emphasize (while stressing the importance of the reported findings) that the retrospective design of this study limits the overall applicability. For example, the median time from first arrhythmic event to echocardiography, during which the markers to predict arrhythmias were explored, was 0.27 years (interquartile range: 0.1 to 5.9 years). This basically implies that a correlation between the 2 is purely hypothetical and that the presence of mechanical dispersion or RVOT dilation does not directly

FIGURE 2 Multimodality Risk Stratification in ARVC



Theoretical disease progression in arrhythmogenic right ventricular cardiomyopathy (ARVC) from genetic predisposition to overt disease fulfilling the 2010 Task Force criteria (TFc). The investigation of exact place of the proposed parameters by Leren et al. (13) is the next step toward improving risk assessment. RV = right ventricle; saECG = signal averaged electrocardiogram.

imply a higher risk of AE on the basis of the findings of this retrospective analysis. Nevertheless, it is likely that these parameters are linked. Indeed, larger ventricles might experience more wall stress, and reduced function (including mechanical dispersion) is likely a result of a significant amount of myocardial fibrosis, both of which are substrates for AE.

How this can be used clinically and what the additional value over the current risk stratification is remains to be determined (**Figure 2**), especially because positive and negative predictive values cannot be obtained from the current data. The precise role of CMR findings, performed in most subjects, is also not evaluated in this study and might add important information about structural alterations (particularly in the left ventricle) that could contribute to arrhythmias in the near future (14).

Optimization of treatment and follow-up strategies in early ARVC remain interesting clinical challenges. In this light, mechanical dispersion deserves further validation. However, we currently do not know what causes these observed functional abnormalities, especially when considering the RV. Are we looking at the result of cardiomyocyte cell loss, fibrosis, delayed cell-to-cell communications by desmosome dysfunction, or perhaps a combination of these? One substrate might prove to be more arrhythmogenic than the other. We believe that this imaging technique will not reach its full potential until the underlying disease substrate causing specific deformation abnormalities is elucidated. After this insight is gained, we potentially have a tool to characterize the affected myocardium. This would ideally lead to a better understanding of its dysfunction and consequently lead to improved risk prediction.

A multimodality approach, as suggested by these authors, definitely makes sense from a pathophysiological point of view, and this publication is not only novel but also very important from that perspective. If no single modality can reliably diagnose this condition, why would the progression of the disease and risk stratification be possible on a single modality? We firmly believe that this complex disease with its variable phenotypic expression requires a "complex" approach during follow-up. It would be extremely interesting to validate these findings in a prospective cohort and, preferably, in a larger and more heterogeneous population at different sites across the globe.

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KEY WORDS arrhythmic risk, arrhythmogenic right ventricular cardiomyopathy, echocardiography, signal-averaged ECG, ventricular arrhythmias