Arrhythmogenic Right Ventricular Cardiomyopathy 2012: Diagnostic Challenges and Treatment

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ARVC 2012. The most common presentation of arrhythmogenic right ventricular cardiomyopathy (ARVC) is palpitations or ventricular tachycardia (VT) of left bundle branch morphology in a young or middle-aged individual. The 12-lead electrocardiogram may be normal or have T-wave inversion beyond V1 in an otherwise healthy person who is suspected of having ARVC. The most frequent imaging abnormalities are an enlarged right ventricle, decrease in right ventricular (RV) function, and localized wall motion abnormalities. Risk factors for implantable cardioverter defibrillator include a history of aborted sudden death, syncope, young age, decreased left ventricular function, and marked decrease in RV function. Recent results of treatment with epicardial ablation are encouraging. (J Cardiovasc Electrophysiol, Vol. pp. 1-5)

Arrhythmogenic right ventricular cardiomyopathy, implantable cardioverter defibrillator, RV dysplasia, sudden death, ventricular tachycardia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by the predominance of ventricular arrhythmias. The presenting clinical manifestations usually consist of palpitations because of premature ventricular beats (PVCs), lightheadedness or syncope because of rapid monomorphic ventricular tachycardia (VT) or uncommonly sudden death as a result of ventricular fibrillation. Symptoms usually appear between the ages of 30–50 but there is a wide range of the onset of symptoms from age 10 to the 80s. Because ventricular arrhythmias usually originate from the right ventricle, the ventricular arrhythmias have left bundle branch morphology. Therefore, suspicion for the diagnosis of ARVC is increased when the ventricular arrhythmias have left bundle branch block (LBBB) morphology and particularly when the QRS axis is superior. This is exemplified by a positive QRS complex in lead AVL indicating an origin from the body of the right ventricle rather than from the right ventricular (RV) outflow tract. Nevertheless, PVCs may arise from the RV outflow tract in ARVC. If so, the diagnosis must be differentiated from patients who have idiopathic VT (RVOT).

Another interesting characteristic of these patients is that their sustained VT may be quite rapid, in the range of 200–250 beats/minute, yet the patients may tolerate this for many hours because the left ventricle has normal or nearly normal function. In patients who present with sustained rapid VT of LBBB morphology the likelihood of ARVC is greatly enhanced if during sinus rhythm the T-waves are inverted in the precordial leads especially in V1–V3 or beyond (Fig. 1). This finding is uncommon in patients who do not have overt heart disease. A caveat regarding the specificity of T-wave inversion in the anterior precordial leads is that T-wave inversion in V1–V4 was found in 12.7% of athletes of black ethnicity. One clue to assist in differentiating these T-wave inversions in healthy black athletes from patients with ARVC is that most (64%) of T-wave inversion in the anterior leads in black athletes were preceded by convex ST segment elevation, an unusual finding in patients with anterior T-wave inversion who have RV cardiomyopathy.

Epsilon waves are low amplitude complexes after the end of QRS complex in leads V1–V3 (Fig. 1). They are uncommonly seen in newly diagnosed patients with ARVC, but are a major diagnostic criterion.

The usual differential diagnosis in patients suspected of ARVC who have PVCs or monomorphic VT arising from the RVOT is that of idiopathic VT. It is important to differentiate these 2 conditions because they have markedly different prognosis. RVOT tachycardia is not an inherited cardiomyopathy. Therefore, family members do not need to be concerned that it will be genetically transmitted. In addition, RVOT tachycardia rarely degenerates into ventricular fibrillation. Therefore, sudden death is not a clinical feature and ICD’s are not indicated for prevention of sudden cardiac death in patients with RVOT tachycardia. The proper identification of these 2 conditions can usually be made clinically. As mentioned previously, patients with RVOT tachycardia do not have a family history of cardiomyopathy and T-wave inversion in V1–V3 or beyond is present in only 4% of patients with RVOT tachycardia but can be seen in 47% of newly diagnosed patients with ARVC. The 12-lead ECG obtained during VT can also assist in properly identifying the etiology of the condition responsible for the RVOT tachycardia.

A QRS duration of >120 milliseconds in lead 1 has a sensitivity of 88–100%, specificity of 46%, positive predictive

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Figure 1. ECG of a 42-year-old woman with ARVC. The T-waves are inverted in V1–V5. An epsilon wave is present (arrow) in leads V1 and V2.

value of 61%, and a negative predictive value of 91–100% for ARVC.\(^6\) The presence of QRS notching in any leads during ventricular tachycardia favors the diagnosis of ARVC.\(^7\)

Electrophysiological testing can assist in the diagnosis. If VT can be induced with multiple LBBB morphologies arising from both the RVOT with an inferior QRS axis as well as from the body of the RV with a superior QRS axis, it greatly favors the diagnosis of ARVC. If the diagnosis is established and if there is a recording of the clinical VT, an electrophysiological study may provide only limited information because there is a strong relation between the cycle length of the clinical VT, induced VT, and follow-up VT (\(R = 0.62–0.88\)).\(^8\)

If an electrophysiological study is performed, additional tests at the time of this procedure may provide useful diagnostic information. These include voltage mapping that can reveal areas of low voltage because of endocardial scar in ARVC that is not present in RVOT tachycardia. However, the absence of low-voltage areas in the right ventricle does not exclude ARVC particularly in the early stage of the disease. This is because the fatty-fibrous infiltrate starts in the epicardium and proceeds to the endocardium.\(^9\) Areas of low voltage may be considerably larger in the epicardium.\(^10\) If low-voltage signals are present in the right ventricle this can aid in localization of the area to perform endocardial biopsy; specifically at the junction of the normal myocardium with the affected areas because the disease may be spotty and a random biopsy may miss the involved area.\(^11,12\) In addition, it is well to avoid biopsy in the center of the ventricular scar because that may be an area that is markedly thin and the risk of perforation may be increased if biopsy is performed in this region.\(^13\) Septal biopsies are not advisable because the typical pathology of RV cardiomyopathy is not usually present in the septum.\(^14\)

An additional useful test that can be done in conjunction with the electrophysiological study is that of a RV angiogram performed in the 30° RAO and 60° LAO views. The protocol for performing this test is provided on the Web site www.arvd.org. During contrast injection it is important to avoid the catheter touching the RV endocardium to prevent the initiation of premature ventricular complexes that can interfere with the interpretation of the angiographic findings.\(^15\)

As previously mentioned, biopsy of the septum is unrevealing for the pathology of ARVC using standard pathological techniques. However, new findings suggest that biopsy of the septum may assist in the diagnosis of ARVC if immunostaining reveals that plakoglobin is not localized to the gap junctions, whereas it is localized to the gap junctions with other cardiomyopathies (excluding giant cell myocarditis and sarcoidosis).\(^16\)

This discussion has focused on the diagnosis of typical ARVC. However, the spectrum of this disease has been expanded because of the knowledge that similar genetic abnormalities can manifest as biventricular involvement or even with a left ventricular (LV) dominant abnormality suggesting dilated cardiomyopathy.\(^17\) In the latter case, a causative desmosomal abnormality is suggested by dominance of ventricular arrhythmias. The new Task Force Criteria have incorporated this finding, and considerable changes have been made to assist the physician to accurately diagnose ARVC.\(^18\) The New Task Force Criteria may be found on the web (www.arvd.org).

Because it is now well known that ARVC is a genetic cardiomyopathy, transmitted primarily as an autosomal dominant disease, the question arises as to the role of genetic testing, either for diagnosis, prognosis, or for identifying family members who may have the disease and may not be symptomatic. The genetic abnormality is associated with structural changes in the desmosomes. Desmosomes are proteins that bind the cells together. Only 30–50% of patients who meet the new Task Force Criteria for ARVC\(^18\) will have an identified genetic desmosomal abnormality.\(^19,20\) This figure is higher if there is a family history of the disease. Importantly, the
absence of a desmosomal genetic abnormality does not ex-
clude the disease. Commercial genetic testing can be used
to identify family members who may or may not be symp-
tomatic and who have a similar genetic desmosomal ab-
normality as the proband. The family member who has the
genetic abnormality is generally advised to avoid engaging
in competitive sports because this is known to facilitate the
onset or progression of the disease. Thus the genetic–phenotypic
relationship is quite variable. Note that 5–20% of patients with
the diagnosis of ARVC may have 2 genetic abnormalities
either located on the same protein such as plakophilin or on
another desmosomal protein. Individuals with 2 desmo-
somal genetic defects have a greater chance of having pheno-
typic expression of the disease and are often more severely
affected. Interpretation of genetic abnormalities is compli-
cated by the fact that up to 16% of normal controls may
have a desmosomal genetic abnormality. Therefore the inter-
pretation of a genetic abnormality must be done with great
cautions, and genetic counseling is recommended.

**Imaging in ARVC**

In patients who are suspected of having RV cardiomyopa-
thy, cardiac imaging studies usually reveal an enlarged right
ventricle with focal wall motion abnormalities. Normal RV
function may be misinterpreted as consistent with general or
local hypokinesis resulting in overdiagnosis. Recognition
of this fact has resulted in modification of the guidelines for
the diagnosis of this disease. To meet imaging criteria for
ARVC the new Task Force Guidelines include a combination
of decreased RV function as well as definite RV wall motion
abnormalities.

Imaging modalities to evaluate RV structure and func-
tion in patients suspected of ARVC include 2-D echocar-
diography, cardiac magnetic resonance (CMR) imaging, car-
diac computed tomography (CT) and angiography. When
these studies are performed, it is important that the techni-
cian focuses on imaging the RV rather than on the LV and
this should be clearly stated in the imaging request from the
referring physician. Suggested protocols for 2-D echocardio-
graphy and CMR are available on www.arvd.org. Experience
with variability in interpretation of imaging studies includ-
ing the CMR indicates that at least 2 imaging modalities
should be performed to confirm if there is an RV imaging
abnormality.

The new Task Force Criteria require both a decrease in
RV function as well as an RV wall motion abnormality that
is more pronounced than “hypokinesis.” This latter term that
was used in the previous Task Force Criteria was not included
in the new Task Force Criteria because of large interobserver
variability. By echocardiography, it has been found that the
RV outflow tract is the most commonly enlarged dimension in
ARVC probands. Guidelines for the echocardiographic
assessment of the right heart has recently been published.

The most important features of the CMR are that it permits
reproducible and standardized quantification of RV volumes
and ejection fraction (Fig. 2). Dynamic images of the RV in
multiple views can be obtained by cine images using a steady
state free precision sequence. Nevertheless, interpretation of
the CMR images, particularly the presence of intramyocard-
dial fat/wall thinning can be misinterpreted.

CMR cannot be used in some patients because of highly
irregular or fast heart rates, claustrophobia, clinically unsta-
able patients, or the presence of a pacemaker or ICD. Under
these circumstances, CT scanning is an imaging alternative.
CT scanning is not a routinely used technique for RV as-
sessment because of significant radiation exposure and the
need to use contrast. Modern CT scanners can now acquire
data with less radiation. In comparison with CMR, CT has
a lower temporal resolution and tends to overestimate end
systolic and end diastolic volumes. CT can show the pres-
ence of regional dysfunction with an accuracy comparable to
CMR (Fig. 3).
Risk Stratification and Treatment

Risk stratification is imperfect. Patients who have documented or even borderline criteria for ARVC are usually treated with ICD’s. In the North American ARVC Registry 77% of newly diagnosed probands or affected family members received this therapy. Although it is well documented from other studies that the majority of probands who had ICDs will have appropriate antitachycardia pacing or shock therapy for VT or ventricular fibrillation, the actual number of lives saved by this approach may be greatly exaggerated. This is because most patients with ARVC have normal LV function and can tolerate sustained VT at rates over 200 beats/minute without syncope or death. Risk factors for ICD therapy in patients with ARVC include a history of aborted sudden death, syncope, young age, decreased LV function, and a marked decrease in RV function. In contrast, family members who have the genetic defect with no clinical manifestations of the disease are at minimal risk and should not receive a defibrillator. A major uncertainty with regard to proper therapy is the young person with ARVC who has frequent PVCs or a history of well-tolerated VT. Implantation of an ICD in these young patients is not without risk because of the long anticipated duration of life with an ICD that can be associated with complications including lead malfunction or ICD pocket or lead infection. A recently introduced ICD that has only subcutaneous lead may be a preferable alternative therapy, but is yet unproven.

A promising approach to therapy for patients with sustained monomorphic VT is catheter ablation. The results of endocardial ablation to prevent arrhythmia occurrence have been disappointing because of the high rate of recurrence of VT. Nevertheless, the recent recognition that the epicardial scar is usually much more extensive than the endocardial area of involvement has resulted in evolution of ablation strategies to involve both the epicardium and the endocardium. Preliminary results are encouraging with success rates of 85% at 3 years. Epicardial ablation is not without hazard because of myocardial perforation, tamponade, etc., and should be done in selected centers that have considerable experience with this approach.

Antiarrhythmic drug therapy to prevent recurrent sustained VT has not been extensively studied except in one relatively small series of patients treated with sotalol and evaluated by electrophysiological studies. Other drugs that have been reported to be effective include amiodarone alone or beta-blocking drugs in conjunction with type IC drugs such as flecainide.

Prevention of the phenotypic expression of the disease, especially with family members with desmosomal abnormalities, needs to be evaluated. There are suggestions from experimental data in knockout ARVC mice that vasodilator drugs such as isosorbide may decrease the progression of RV enlargement. In addition, excessive exercise appears to exacerbate the manifestations in the disease in experimental animals. The preventive approach of treating family members with genetic ARVC defects using beta-blockers or ACE inhibitors is reasonable but there are no clinical supportive data. Prevention of RV dilatation should be a fruitful area of research. Research in ARVC is now focusing on understanding the genetics and molecular basis of the disease.

In summary, the diagnosis of ARVC can often be suspected on the basis of ECG abnormalities. It is difficult to accurately interpret imaging studies of the right ventricle because of its irregular structure and lack of symmetrical pattern of contracture. Commercial genetic testing is available but the results must be interpreted with caution because only 30–50% of patients with ARVC have an identifiable genetic abnormality and individual patients may have more than one desmosomal defect. Risk stratification is imperfect, but it is clear that high-risk patents should be treated with an ICD. Improved methods of catheter ablation are promising.

References