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Arrhythmogenic right ventricular cardiomyopathy – not just a matter of fat

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Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia, is an inherited cardiomyopathy associated with arrhythmia, heart failure, and sudden cardiac death (SCD). Considerable strides have been made in understanding the pathogenesis, genetics, and diagnosis of ARVC, since it was first described over 20 years ago. Recognizing this clinical entity and screening asymptomatic family members for this condition are vital in order to prevent SCD. To accomplish this entails knowledge of the salient diagnostic features of this rare condition. This issue of *Cardiology Rounds* provides a contemporary review of the clinical features, diagnosis, and management of ARVC.

The prevalence of ARVC in the general population is estimated at approximately 1 in 5000;[1] however, the lack of a "gold standard" for diagnosis may underestimate the true disease prevalence. While rare, ARVC accounts for approximately 2.2% of adult SCDs in the United Kingdom,[2] 5% of SCDs in young individuals < 35-years-old in the United States,[3] and 25% of exercise-related deaths in the Veneto region of Italy.[4] The disease rarely manifests before adolescence and affected individuals are often men with an active lifestyle.

Pathology

Since ARVC is not well-defined and has variable clinical presentations, it is not surprising that controversy surrounds the histological features of the disease. The most prominent pathological finding involves the loss of right ventricular myocardium with fibrofatty replacement. However, the presence of fat alone is the least reliable criterion for diagnosis of ARVC, and should be used in conjunction with other histological features.

Most normal hearts contain epicardial fatty tissue. This tissue is increased in obese individuals[5] and women.[6] While the inner myocardium and subepicardial fat layer are usually distinct, fatty infiltration of the underlying myocardium may occur, particularly, at the anterolateral and apical regions of the right ventricle (RV).[7] The clinicopathological significance of a fatty, infiltrated RV remains to be established.

In ARVC, portions of the RV are replaced with fibrofatty tissue. Residual myocytes are interspersed between adipocytes and fibrous tissue. Higher magnification of the tissue often reveals hypertrophy and/or degeneration of the remaining myocytes with dystrophic nuclei, in addition to fibrous tissue and inflammatory cell infiltrates – features not seen in the normal fatty-variant RV.[7]

Two variants of ARVC have been described – *fatty* and *fibrofatty*.

- **In the *fatty* variant,** transmural infiltration of the myocardium with fat occurs and, in some cases, may result in pseudohypertrophy of the RV. This variant rarely affects the left ventricle (LV) and spares the interventricular septum. Small islands of fibrosis are present on high-power histological analysis, but may be missed with inadequate sampling.
- **In the *fibrofatty* variant,** the right ventricular walls are classically thinner and translucent with extensive replacement by fibrotic tissue. Involvement of the ventricular septum and LV is also more common with this variant.[7] Extensive fibrosis appears to be associated with electrical instability, whereas fatty infiltration is associated with developing heart failure.

Given the difficulties in sampling, the presence of fatty myocardial infiltration in normal myocardium and the presence of fibrosis in other cardiomyopathies, the histological diagnosis of ARVC can be challenging. Experience with autopsy samples is well established. However, the value of endomyocardial biopsy is still undefined and the technique has specific limitations, including the inability to obtain full thickness specimens and the predominant sampling from the interventricular septum that is

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classically spared in ARVC. Angelini and colleagues examined the yield of right ventricular endomyocardial biopsies in 30 patients with known ARVC, and compared these with biopsy findings in controls and patients with dilated cardiomyopathy. Their results suggest that an RV endomyocardial biopsy may be diagnostically helpful if there is the co-existence of fatty tissue involving at least 3% of the myocardium and fibrose tissue exceeding 40%; these percentages are highly suggestive of an ARVC diagnosis (sensitivity 67%, specificity 92%).[8]

Some experts recommend routine endomyocardial biopsies in patients with suspected ARVC because it may provide a definitive diagnosis in approximately one-third of patients and may exclude diseases that mimic ARVC (eg, myocarditis or sarcoidosis).[9] However, given the low yield and lack of test sensitivity, other specialists do not advocate routine endomyocardial biopsy.[10]

Histological changes result in morphological alterations of the RV that frequently involve the high-stress areas at the thinnest portion of the RV – the "triangle of dysplasia" (ie, bounded by the right ventricular inflow, outflow, and apex). Akinetic, dyskinetic, or aneurysmal areas may be particularly observed within this triangle. Dilation of the RV, particularly the right ventricular outflow tract (RVOT), may also occur. Finally, trabecular disarray and trabecular hypertrophy result in the angiographic finding of deep fissures with a "pile d'assiettes" (stack of plates) appearance of the RV.[11] Left ventricular involvement has been reported in up to 76% of cases,[12] with a predilection for the postero-septal and postero-lateral walls – also areas of high mechanical stress within the LV. Occasionally, extensive left ventricular involvement may mimic a dilated cardiomyopathy.

Genetics

Approximately 30% to 50% of ARVC cases have a familial component and families in France, Italy, Greece, and North America, have been identified. Within Canada, a Newfoundland founder family and 10 subsequent families have been described with autosomal dominant ARVC.[13] Overall, 10 gene loci have been identified and the gene products of 5 have been determined.[14] All, with the exception of Naxos disease and a variant of ARVC8, are autosomal dominant (AD) (Table 1).

Mutations involving the gene for the cardiac ryanodine receptor (RYR2/ARVC2) have been characterized. This receptor plays a vital role in myocyte calcium (Ca^{2+}) handling and the RYR2/ARVC2 mutation is hypothesized to result in unstable Ca^{2+} handling in the myocyte, especially under conditions of increased sympathetic tone. This may potentially explain the effort-induced arrhythmias described with ARVC. Increases in intracellular Ca^{2+} levels predisposing to arrhythmias are likely due to the genesis of delayed after-depolarization. In addition, these increased levels may trigger myocyte apoptosis resulting in myocardial cell death and fibrofatty replacement.[14]

Unlike the RYR2/ARVC2 mutation that affects an intracellular ion channel, non-ion channel mutations have been identified. Specifically, ARVC8, ARVC9, and Naxos disease, all encode for mutations involving gene products comprising the cardiac desmosome. Desmosomes are specialized structures providing a mechanical attachment between cardiac myocytes. It is hypothesized that under conditions of mechanical stress, impaired desmosomal function can result in myocyte detachment, death, and a resulting inflammation. Given the limited capacity for cardiac regeneration, fibrofatty replacement occurs.[15] This hypothesis may shed light on the hallmark features of ARVC; specifically, as wall tension is inversely proportional to wall thickness (Laplace's law), the thin-walled RV (especially within the triangle of dysplasia) will be exquisitely vulnerable to desmosomal defects.

Table 1: Genes associated with ARVC[14]

Gene	Protein	Inheritance mode	Chromosomal location
ARVC1	TGF-b3	AD	14q23-24
ARVC2	RYR2	AD	1q42-43
ARVC3	NA	AD	14q12-22
ARVC4	NA	AD	2q32.1-32.3
ARVC5	NA	AD	3p23
ARVC6	NA	AD	10p12-14
ARVC7	NA	AD	10q22
ARVC8	Desmoplakin	AD/AR	6p24
ARVC9	Plakophilin-2	AD	12p11
Naxos disease	Plakoglobin	AR	17q21

AD = autosomal dominant; AR = autosomal recessive

Finally, although ARVC1 was the first chromosomal locus linked to ARVC, only recently has a possible gene product been identified. This mutation is hypothesized to result in increased production of the cytokine transcription growth factor beta-3 (TGF-β3). This cytokine may play a role in the excess formation of cardiac fibrosis[14] and subsequent development of ARVC. Since this mutation results in increased cytokine production, it is unclear why the RV is preferentially affected.

Significant variability in disease penetrance has been noted, supporting questions on the presence of allelic heterogeneity and non-genetic factors (eg, inflammatory, infectious, or degenerative processes) that may facilitate gene expression. A complex interaction likely exists.

Clinical presentation

Generally, ARVC has a predilection for males who typically present prior to age 40. The diagnosis should be considered in young patients with syncope due to ventricular tachycardia (VT), cardiac arrest, or adult patients with congestive heart failure.[16] While 30%-50% of ARVC cases are familial, incomplete penetrance results in variable disease manifestations; thus a wide disease spectrum is present. Classically, 4 phases of ARVC have been described.[17]

- The *silent phase* is associated with minimal symptoms, infrequent ventricular premature beats or tachycardia, and minimal changes on noninvasive imaging.
- The *self-evident phase* is characterized by the presence of sustained VT as well as structural abnormalities involving the RV.
- The *right ventricular phase* is characterized by the development of progressive dilation and loss of RV contractility.
- The development of *biventricular heart failure* occurs due to the progressive involvement of the left and right ventricles.

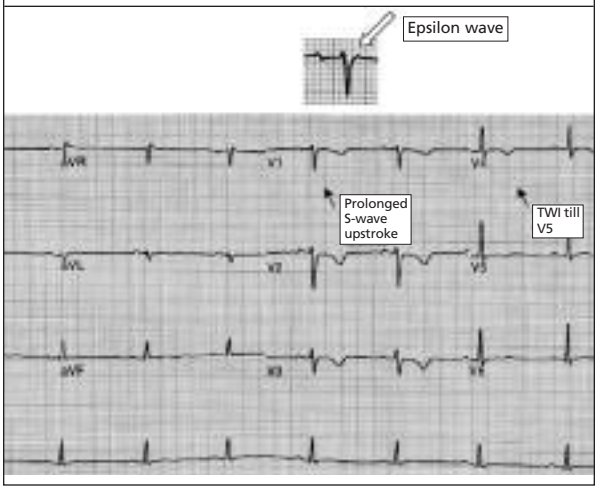
Arrhythmias are of left bundle branch block (LBBB) morphology, reflecting their genesis within the RV. Patients may present with frequent ventricular premature beats, sustained VT, or cardiac arrest. VT, which is most commonly due to

Table 2: Diagnostic criteria for ARVC

	Major	Minor
Family history	• Family disease at autopsy	• SCD in patient <35 yrs old suspected due to ARVC • Family history
ECG changes	• Epsilon Waves	• Late potentials on SAECG • Inverted T waves (V2-3)
Arrhythmias		• Sustained or non-sustained LBBB VT • Frequent VPB (>1000/24hrs) on Holter
Ventricular dysfunction	• Severe dilation and reduction of RV EF (with no or mild involvement of LV)	• Mild global RV dysfunction/ reduction in EF • Segmental RV dilation/ hypokinesia
Tissue characterization	• Fibrofatty replacement of the myocardium on endomyocardial biopsy	

SCD = sudden cardiac death; SAECG = signal-averaged ECG; LBBB VT = left bundle branch block ventricular tachycardia; VPB = ventricular premature beats; RV = right ventricle; LV = left ventricle; EF = ejection fraction

Figure 1: Typical ECG of a patient with ARVC[9]



TWI = T-wave inversion

macro reentry circuits involving islands of fibrofatty tissue, is frequently precipitated by an increase in sympathetic tone.

Heart failure symptoms (predominantly isolated RV failure) may also develop in individuals with ARVC, typically in the 4th and 5th decades of life.[1] ARVC is one of a few myocardial diseases that results in RV failure in the absence of pulmonary hypertension. Right heart failure often presents within 4 to 8 years after the development of a complete right bundle branch block (RBBB).[18] Patients may present with biventricular failure. Left-sided heart failure is often due to progressive fibrofatty replacement of the LV. Patients presenting with biventricular failure may be inappropriately diagnosed with dilated cardiomyopathy. Distinguishing between dilated cardiomyopathy and ARVC is important because patients with ARVC are more prone to arrhythmic events.

Hulot et al examined the natural history of a French cohort of patients with ARVC followed between 1977 and 2000 (mean follow-up ~ 8.1 years). An average mortality rate of 2.3%/year was noted. After multivariate analysis, only the presence of RV failure and LV failure predicted cardiovascular (CV) mortality (odds ratio [OR] of CV death = 13.7 and 10.8, respectively). Interestingly, while the presence of arrhythmias or syncope was associated with an increased risk of CV death on univariate analysis, these features did not predict future events when examined in a multivariate model.[19]

Diagnosis

Since no diagnostic "gold standard" exists, the diagnosis of ARVC remains problematic.[20] Presently, a diagnosis is established based on criteria determined by the Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology.[21] These criteria, shown in Table 2, recommend noninvasive testing (eg, electrocardiogram [ECG], signal-averaged ECG, Holter monitoring, and echocardiography), in addition to obtaining a family history to determine the possibility of an ARVC diagnosis. A diagnosis of ARVC is made when a patient demonstrates 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria. If the clinician has a high index of suspicion, further testing, including cardiac magnetic resonance imaging (MRI), endomyocardial biopsy, and electrophysiological testing, may be considered.

While the established Task Force criteria are capable of allowing homogenous study groups to be assembled, they are still imperfect and have yet to be prospectively validated in a large cohort. According to one editorialist, "conformity does not necessarily mean accuracy."[20] Additional imaging studies may be helpful for the diagnosis, but they also have limitations. Molecular diagnosis may be the future gold standard diagnostic test; however, at the present state of knowledge, premorbid genetic testing is unlikely to be very helpful because, thus far, it has elucidated only a minority of ARVC cases. With enhanced knowledge of the disease, genetic testing may become a promising method for diagnosis. In the absence of a gold standard, clinical assessment with frequent reassessment seems logical.

Electrocardiogram: ECG changes are noted in up to 90% of patients with ARVC.[17] These changes reflect depolarization and repolarization abnormalities localized over the right precordial leads. The most common ECG change is T-wave inversion in the right precordial leads (leads V1-V3; Figure 1). While this finding may be present with an RBBB, congenital heart disease, or in African Americans or children aged <12 years (both normal variants), its presence, especially when extending beyond lead V3, should raise suspicion for ARVC. In addition, the magnitude of T-wave inversions may be correlated with the degree of the RV dilation.[22]

Slowed conduction through the RV due to islands of fibrofatty tissue interspersed between normal myocardium, may manifest on the surface ECG as selective QRS prolongation of at least 110 milliseconds (ms) within the right precordial leads (V1-V3), in the absence of an RBBB. The presence of at least a 50 ms difference in QRS duration between right and left precordial leads (ie, QRS dispersion) is highly suggestive of ARVC,[23] and predictive of massive right ventricular dilation and a high risk for recurrent ventricular arrhythmias.[24]

Epsilon waves (Figure 1) also represent delayed conduction within the RV. These small waves occur at the end of the QRS complex, and represent fragmented and delayed low-amplitude potentials within the terminal portion of the QRS complex also due to islands of fibrofatty tissue in normal myocardium. While highly specific, this finding is only present

in ~30% of patients with ARVC. Further elucidation and characterization of late potentials may also be obtained with signal-averaged ECG.

Ventricular arrhythmias: Ventricular arrhythmias with an LBBB pattern suggest a right ventricular origin. While QRS morphology reflects the site of the arrhythmia (ie, the superior axis reflects the infundibulum, whereas an inferior axis suggests the RV inferior wall), different morphologies may be present with ARVC, given the diffuse nature of the disease. Once the diagnosis of an LBBB VT is made, patients must be assessed for alternative diagnoses, including congenital heart disease, a Mahaim bypass tract, as well as benign RVOT-VT.

Imaging of the RV: Imaging of the heart is an integral component of the diagnostic workup since it permits identification of morphological abnormalities in the RV and excludes other forms of structural heart disease. Structural abnormalities in ARVC may be segmental or diffuse. Functional abnormalities may range from mildly impaired contractility to severe global hypokinesis. In addition, RV hypertrophy and trabeculations have been noted.

An optimal imaging modality should have the ability to adequately image all portions of the RV, obtain objective information (eg, volume and ejection fraction [EF]) that may be followed serially, and possibly provide information on tissue characterization. While limitations exist for all current noninvasive imaging modalities, advances in the near future are promising. However, it is unclear whether the typical ARVC findings on imaging have any utility when individuals do not achieve Task Force diagnostic criteria, or whether the absence of any imaging abnormalities is sufficiently strong enough to identify a low-risk group of patients. Finding the answers to these questions is critical because the presymptomatic phase of the disorder may have minimal clinical findings, but still a finite risk of SCD.

Echocardiography: By virtue of its widespread availability, low cost, ease of performance and interpretation, 2-dimensional echocardiography has become a frequently employed tool for establishing the diagnosis of ARVC. Adequate visualization of the RV is not always satisfactory, especially in the setting of chest wall disease or obesity, and limits the utility of this investigation. However, the use of contrast and 3-dimensional echocardiography may allow enhanced RV visualization and improve the assessment of its size, shape, and wall-motion abnormalities to increase accuracy and reproducibility.[25,26] Enhancements in echocardiography may also permit accurate quantification of right ventricular volumes and EFs allowing for serial follow-up.

Recently the Multi-Disciplinary Study of Right Ventricular Dysplasia investigators quantified echocardiographic abnormalities in 29 probands with Task Force diagnosed ARVC.[27] In this homogenous group of patients, echocardiographic abnormalities were common. An enlargement of the RVOT was the most common finding in patients with ARVC (89% of patients had a diastolic RVOT dimension in the parasternal long axis view >30 mm). Global RV abnormalities were noted in more than two-thirds of the population, while the presence of any RV dysfunction was noted in 82%. The authors recommend that dilation of the RV that is >30 mm in diastole in the parasternal long axis view (visualization is poor in apical views) should be the primary echocardiographic parameter quantified when the disease is suspected.[27]

Magnetic resonance imaging: Despite issues surrounding its sensitivity, specificity, and inter-observer reliability, MRI is evolving as a promising technique for assessing ARVC. As mentioned above, one limitation of traditional echocardiography (and also radionucleotide ventriculography) is the inability to provide a multiplanar assessment of the RV with its relatively complex geometry. MRI may be better suited to imaging the RV, depicting it in 3 dimensions and thereby facilitating quantitative assessment (ie, RV volume and EF). Cine-angiography also permits the assessment of RV wall motion abnormalities.[28] Thinning of the RV wall frequently occurs with ARVC, but this finding is difficult to assess with MRI due to motion artifacts. In addition, a loss of the distinction between normal epicardial fat and the RV myocardium may also affect the assessment of RV wall thickness.[29]

One of the main advantages of MRI is its ability to provide tissue characterization of the myocardium. T1-weighted imaging has been used to identify myocardial fat because the presence of high-signal intensity is a strong indication of fatty infiltration. However, Bluemke et al demonstrated high rates of inter-observer variability for detecting myocardial fat with cardiac MRI.[30] This observation is not surprising given the lack of spatial resolution with the thin-walled RV, as well as the presence of normal epicardial and pericardial fatty tissue that may often mimic intramyocardial fat.[29]

Recent work has suggested that the use of a gadolinium-based contrast agent may permit visualization of fibrotic areas within the RV, another pathological feature of ARVC. Tandri et al studied 12 individuals with ARVC and noted an excellent correlation between myocardial delayed-enhancement MRI and histopathology, as well as with induction of VT.[31] Further experience with this technique is needed.

Overall, as MRI techniques evolve, this modality may play a more prominent role in diagnosing ARVC given its noninvasive nature, lack of ionizing radiation, and ability to provide structural and functional information, including possible tissue characterization. It is unlikely to be the sole imaging modality, however, due to the increasing use of cardiac defibrillator (ICD) therapy in patients with ARVC, which is a contraindication to MRI use. In order to avoid over-diagnosis, clinicians must be aware of the limitations of this technique and recall that the diagnosis of ARVC is a clinical one and not based solely on MRI findings.[32] Considerable expertise is required when interpreting MRI scans for ARVC. Since this disease is rare, it is preferable that interpretations be made at imaging centres with expertise in ARVC.

Computed tomography: Although used infrequently, cardiac computed tomography (CT) may be useful for characterizing the RV. CT scanners are easily accessible, fast, have reliable image quality (which may be enhanced with the use of contrast), and have the ability to reformat images in 3-dimensions, allowing for accurate quantitative information. Similar to MRI, tissue characterization

(particularly of myocardial fat) is possible.[29] CT may be advantageous in the serial follow-up of patients with known ARVC and an implantable cardioverter defibrillator (ICD), which precludes MRI imaging. However, the presence of ionizing radiation makes MRI a more appealing screening tool (especially when screening young females).

Right ventricular angiography: While RV angiography has been considered the "gold standard" for diagnosing ARVC, it should simply be considered an additional modality for determining RV structure and function. Particular attention should be paid to the RV apex, outflow tract, and anterior wall (where the "stack of plates" may be observed) when performing ventriculography. Standard views include a 60° left anterior oblique (LAO) with a 30° cranial tilt, as well as 30° right anterior oblique (RAO) with a 20° caudal tilt, although nonstandard views such as an anteroposterior or left-lateral view may be necessary.[33]

Electroanatomic mapping: Limitations in all imaging modalities may hinder the diagnosis in individuals with a "forme-fruste" of the condition that demonstrates minimal structural abnormalities. In addition, a definitive pathological diagnosis may not be possible with an endomyocardial biopsy. Additional information may be obtained with electro-anatomic mapping. Three-dimensional electroanatomic mapping can produce an electro-anatomic voltage map of the RV. Areas with low-amplitude, longer-duration intracardiac electrograms reflect areas of myocardial replacement with fibrofatty tissue. These characteristic electrograms are distinctly different from those produced in normal myocardium and can identify the presence and extent of pathological myocardium that may then be correlated with imaging findings.[34-36]

Treatment

Pharmacological therapy: Many individuals with ARVC experience ventricular arrhythmias on exertion; thus, individuals identified with the disease should be counseled to avoid strenuous activity. In addition, β-blocker use seems reasonable for blunting sympathetic stimulation. Otherwise, the efficacy of antiarrhythmic drugs is largely anecdotal, with drug efficacy reported only in small retrospective studies.[9,33] Regardless, a high recurrence rate of arrhythmias occurs in patients on drug therapy alone. As a result, the role of standard heart failure medications and anticoagulation is not clear in these individuals.

Catheter ablation: Catheter ablation may be considered in some patients either as primary therapy or in addition to ICD therapy (particularly in patients with multiple ICD discharges over time). Successful ablation is common; however, recurrence is also common due to the progressive nature of the disease.[9] In addition, multiple VT morphologies originating from multiple foci may limit the success of ablation.

Implantable cardioverter defibrillators: Evidence exists supporting a role for ICDs in the primary and secondary prevention of SCD for a variety of patient populations, in whom there is a lack of efficacy with antiarrhythmic drugs. To date, only limited case series have reported the potential benefit of ICDs in patients with ARVC. The results are promising and suggest that there is a similar SCD risk reduction as that observed in other populations.[37] For example, over a follow-up of 39 months, Corrado et al reported a 96% survival rate in 124 patients with ARVC who received an ICD for secondary prevention of SCD.[38] Twenty-four percent of these individuals received ICD therapy for ventricular fibrillation or ventricular flutter, ie, fatal arrhythmias. Thus, 24% of patients evaded SCD, thereby, improving overall survival.

Hodgkinson and colleagues compared 48 individuals with the ARVC5 mutation, who received ICD implantation for the primary prevention of SCD, to historical controls with the same documented mutation and no ICD.[39] Similar to Corrado's findings in a secondary prevention population, the 5-year mortality was 28% in the high-risk control group with no ICDs, compared with 0% in the group receiving ICDs. Moreover, the survival curve comparing the time to first ICD therapy for ventricular fibrillation or fast VT with the survival curve in patients not receiving an ICD was similar, suggesting that a hypothetical death was averted with ICD therapy at a time when actual death occurred in individuals without an ICD. Since this study involved a specific genetic subpopulation (ie, all with ARVC5), it is unclear whether these results are applicable to the general ARVC population, given the heterogeneity of the disease.

The results of these and other studies are encouraging; however, ICD implantation is not without complications in this younger population. For example, higher pacing thresholds and lower amplitude of sensed electrical potentials may exist due to the fibrofatty replacement of the RV. Moreover, these parameters may change with time and disease progression. Lead perforation through the thin-walled RV is possible. Finally, this younger population may require several lead (due to lead fractures) and generator (due to battery exhaustion) changes during their lifetime. Further work into appropriate clinical and genetic risk stratification methods may aid with defibrillator decision making.

Family screening: The diagnosis of ARVC has implications for the individual patient and their first-degree relatives. Given the risk of SCD and the predominantly autosomal dominant mode of inheritance, assessment for the disease in all first-degree relatives is of vital importance. Moreover, periodic reassessment is necessary for family members who fail to fulfill diagnostic criteria on initial assessment. Further knowledge of the genetic mechanisms of the disease may allow for more efficient screening.

Conclusion

ARVC is a rare, progressive cardiomyopathy associated with ventricular arrhythmias and heart failure. Ongoing research, including that by the multi-centre Multidisciplinary Study of Right Ventricular Dysplasia (supported by the National Heart Lung and Blood Institute and the National Institutes of Health), will ensure that genetic, imaging, and therapeutic advances are made in the years to come.

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Upcoming meetings

21-26 October 2006
Canadian Cardiovascular Society – CCC 2006
Vancouver, British Columbia
Contact: www.ccs.ca

12-15 November 2006
American Heart Association Scientific Sessions 2006
Chicago, Illinois
Contact: www.scientificsessions.org

11-15 March 2007
23rd Annual Cardiovascular Conference Lake Louise
Fairmont Chateau Lake Louise Hotel,
Lake Louise, Alberta, Canada
Contact: www.acclakelouise.com

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