Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a syndrome characterized by myocardial disease, predominantly involving the right ventricle (RV) and associated with ventricular tachycardia arising from this chamber (left bundle branch block [LBBB] morphology), syncope, and sudden death. At autopsy, there is an unusual distribution of fatty and fibrotic tissue within the RV, preferentially affecting 3 areas, namely, the apex, the inflow tract, and the outflow tract.1,2 In typical cases of ARVC there is evidence of a familial trait, but this may only be revealed when relatives are examined directly.3 Clinical genetic studies performed to date have established that ARVC is not a single disorder but a syndrome consisting of multiple entities with discrete clinical features. There is significant variation in the natural history of the underlying diseases, but there is also substantial pleiotropy of clinical expression of the same single disease gene segregating within individual families.3,4 The mutated genes identified so far strongly suggest that ARVC is the result of perturbation in specialized intercellular adhesion junctions known as desmosomes,5–17 and thus is mechanistically distinct from either hypertrophic or dilated cardiomyopathy.18

Data-driven diagnosis and management are difficult in rare disorders. These problems are further compounded in ARVC, where the causal heterogeneity results in differential representation of specific forms of the disease in smaller studies. This representation is particularly problematic in inherited diseases whereby many individuals in smaller series are likely to be related. As the RV has become more accessible through improved imaging techniques, the number of individuals diagnosed with ARVC has increased substantially. However, it is clear that many subjects who carry the label of ARVC exhibit a natural history different from that seen in early reports.19 It remains unclear whether this is the result of the inadvertent inclusion of discrete disorders and normal variants or the reflection of a reservoir of ARVC in which ventricular arrhythmias and sudden death are infrequent complications. The investigation and management of this expanding group of indeterminate patients is now a common clinical dilemma.
International registries have been established, but will take time to accumulate the numbers and outcomes data required to make rigorous conclusions.20–22

These problems led to the proposal of standardized diagnostic criteria by an international Task Force in 1994 (Box 1).23 Multiple disease features were classified as major or minor by consensus, and an empiric scoring system was developed incorporating insights from autopsy studies, noninvasive investigation, and family studies. However, the original criteria and subsequent proposed modifications were defined retrospectively from aggregated series of referrals to tertiary care institutions and have never been prospectively validated as was originally intended.3,23,24 The criteria are increasingly applied in situations where the prior probability of ARVC is different from the initial derivation set of patients, and thus the sensitivity and specificity of the scoring system are less robust than anticipated.3,19 This difference is highlighted by recent genetic work whereby it

<table>
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<th>Box 1</th>
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<td><strong>Task Force criteria, qualifiers, and limitations</strong></td>
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</table>

**Family history**

**Major:** familial disease confirmed at necropsy or surgery

- Evaluation should be done by a cardiac pathologist.

**Minor:** family history of premature, sudden death or of clinical diagnosis based on present criteria

- Clinical and autopsy data (if available) from premature, sudden deaths should be reevaluated by a specialist.

**Electrocardiographic (ECG) depolarization or conduction abnormalities**

- ECG criteria are particularly dependent on prior probability of ARVC.

**Major:** epsilon waves or localized prolongation of QRS (>110 ms) in right precordial leads

**Minor:** late potentials on signal-averaged ECG

**ECG repolarization abnormalities**

- ECG criteria are particularly dependent on prior probability of ARVC.

**Minor:** inverted T waves in right precordial leads in individuals older than 12 years in absence of right bundle branch block

**Arrhythmias**

**Minor:** sustained or nonsustained LBBB-type ventricular tachycardia documented on ECG, Holter or during exercise testing; frequent ventricular extrasystoles (>1000/24 hours on Holter)

**Recent data suggest electrophysiology study (EPS) may be helpful in discriminating between ARVC and right ventricular outflow tract tachycardias.**

**Global or regional right ventricular dysfunction or structural abnormality**

**Reproducible quantitative indices of RV function (using magnetic resonance imaging [MRI], computed tomography [CT], cardiac catheterization, or echo) remain specialist tools.**

**Major:** severe dilatation and reduction of RV ejection fraction with minimal or no left ventricle (LV) involvement; localized right ventricular aneurysms (akineti c or dyskinetic areas with diastolic bulging); severe segmental dilation of RV

**Minor:** mild global RV dilatation or reduction in ejection fraction with normal LV: mild segmental dilation of RV; regional RV hypokinesis

**Tissue characteristics of walls**

**Major:** fibrofatty replacement of myocardium on endomyocardial biopsy

**Biopsy is insensitive, but may help exclude other disorders restricted to RV. MRI tissue characterization was not included in original criteria.**

Note that for at-risk relatives of definitively affected probands, virtually any cardiac abnormality may represent ARVC. This representation does not imply that the clinical course will be similar to the probands or other definitively affected individuals.
was demonstrated that Task Force criteria were poor predictors of carrier status in family members. In the setting of familial disease, where the prior probability of ARVC may approach 0.50, the original Task Force criteria are greatly reduced in sensitivity, and modifications already have been proposed. Conversely, in the context of incidental clinical abnormalities the criteria lack specificity, and the number of indeterminate individuals generated by their application suggests that a comprehensive reevaluation is necessary, particularly to determine thresholds for implantation of cardioverter defibrillators.

In this article, focus is on diagnosis and management of ARVC, while highlighting central issues in the rigorous assessment of RV disease and emphasizing the practical management of indeterminate individuals. The investigators have concentrated on larger published series that are less likely to have been distorted by referral biases or local genetic founder effects, and have deliberately excluded current dogma based on small studies that are difficult to interpret. This approach is intended not to be nihilistic but to avoid overstatement of current knowledge while highlighting areas for future investigation.

CLINICAL PRESENTATION AND NATURAL HISTORY

The defining reports in ARVC were pathologic series based on premature sudden deaths. Modern pathologic studies suggest that ARVC is the primary cause in as many as 10% to 15% of cases of sudden death in those younger than 65 years, but nonischemic causes are likely to be overrepresented in these data. Unheralded cardiac arrest remains the typical mode of presentation for a substantial subset of those with ARVC. Not surprisingly, clinical series based on antemortem diagnosis offer a more varied picture (Box 2). The largest studies suggest that most living ARVC patients present with palpitations or presyncope, whereas as many as one-third would have had a documented syncopal episode. Less common presentations include ventricular tachycardia originating in the RV, isolated and unexplained RV failure, or even biventricular heart failure. Clinical screening of the families of probands with definitive ARVC also identifies significant numbers of asymptomatic but affected relatives. Perhaps more common than these groups is the increasing number of individuals with 1 or more incidentally discovered abnormalities suggestive of ARVC, but in whom no definitive diagnosis is possible. The combined prevalence of each of these clinical entities is unknown, but in aggregate is likely to be considerably more common than suggested by autopsy series.

As might be expected from the range of potential presentations, there are few long-term follow-up studies of definitively affected ARVC subjects, and those that do exist are confounded to variable degrees by selection bias, causal heterogeneity, and local genetic founder effects. Only 3 follow-up studies include more than 45 subjects, and these serve to illustrate the fundamental problems intrinsic to the study of this rare, familial syndrome. Hulot and colleagues followed 130 selected patients for a mean of 8 years and noted an annual mortality rate of 2.3%, largely from progressive heart failure. In contrast, a follow-up of 151 affected relatives revealed electrocardiographic and echocardiographic evidence of progression, but only 1 individual died over an 8-year period, indicating an annual mortality rate of only 0.08%. In this series, there were no episodes of clinical heart failure. These 151 subjects represented only a few causal genotypes as multiple families mapped to the same loci, and there was clear evidence of local genetic founder effects. Most recently, the initial experience with 100 subjects from Johns Hopkins was reported confirming the substantial variation in presentation and natural history seen in other studies.

These data strongly suggest that smaller studies are likely to be heavily weighted in favor of specific forms of ARVC or individual ARVC families, and thus are nonrepresentative of the syndrome as a whole. Many of the disparities seen in the ARVC literature are likely to reflect this underlying causal heterogeneity.
are varying reports of a marked gender bias in the risk of sudden death, but these are most notable in single families and not seen in unselected populations.

PATHOLOGY

Pathologic examination is the effective gold standard in ARVC, but correlation with antemortem clinical features has proven difficult. The original descriptions of ARVC focused on the fatty replacement seen in the RV. The use of the term replacement infers that the muscle develops normally, and subsequently undergoes dysplastic degeneration with replacement of muscle by fibrous scarring and fatty tissue. Although this sequence of events has never been conclusively demonstrated, progressive deterioration of RV structure and function undoubtedly occur. Focal RV wall thinning and RV aneurysms have been reported on gross pathologic examination, and are considered by some investigators to be pathognomonic of ARVC.

Histologic examination reveals a range of myocardial injury and repair similar to that seen in other forms of cardiomyopathy. Aside from the chronic stage at which isolated myocytes are seen within large tracts of fibrous tissue and adipocytes, there are no unique microscopic features. Some investigators have made distinctions between bland adipose replacement and fibrofatty disease with inflammatory infiltrates, but whether these represent distinct clinical or biologic entities remains unclear. There are studies suggesting that inflammatory infiltrates are more common in the context of sudden death, and recent work has demonstrated evidence of RV apoptotic activity in individuals who have died. There is important histologic evidence of fibrofatty involvement of the left ventricle (LV) in a significant proportion (30%–75%) of ARVC cases. Similar histologic findings restricted to the LV also have been seen in so-called arrhythmogenic LV cardiomyopathy.

Ultimately, large prospective studies may be able to address the relationship between the clinical and pathologic features of ARVC, but at present only retrospective data exist. Tabib and colleagues defined the circumstances of death associated with gross and microscopic evidence of ARVC in 200 individuals. These cases represent approximately 10% of the unexpected sudden cardiac deaths in a large municipal autopsy series. Most individuals in this series died suddenly during daily activities, with a small number of subjects collapsing during exercise (3.5%). Most died in their forties, but only 6 individuals had any arrhythmia diagnosed before death, and none of those who died suddenly from ARVC had suffered any symptoms of heart failure. This study is the largest single series of definitive ARVC cases and offers several important insights. Fatty replacement in virtually all cases extended from the septum or anterior interventricular groove into the anterior RV wall to a variable extent (correlation with magnetic resonance imaging [MRI] is seen in Fig. 1A and B). Fibrofatty lesions were restricted to the external margin of the RV in only 2% of cases. Other notable findings were the unusually wide distribution of heart weights, which was not reflected in the normal mean values. Although rarely noted in other studies of ARVC, significant left ventricular hypertrophy was seen in 15% of subjects and was particularly prevalent in younger age groups. The predominant histologic lesions seen were fine interstitial fibrosis and adipose replacement. Fibrosis involved the His bundles in most of the hearts studied. Inflammatory infiltrates were rare and, when present, were sparse. LV involvement was present in around 30% of cases but was largely fibrotic rather than adipose in nature, correlating closely with heart weight. Smaller series have identified more frequent LV involvement and more impressive inflammatory infiltrates.

Taken together, these data serve to highlight the problems correlating rigorous, pathologically confirmed ARVC with clinical features other than sudden death. Many of the current problems in diagnosis and management reflect the lack of a gold standard in most clinical studies of ARVC. Progress in the field depends on establishing a tight relationship between each of the constituent clinical entities within ARVC and the underlying gross, microscopic, or molecular pathology.

GENETICS

Clinical Genetics

Early in the study of ARVC, it became evident that many of the relatives of probands also exhibited arrhythmias, syncope, or sudden death. Systematic studies of family members suggest that up to 50% of individuals with ARVC have evidence of a Mendelian disease. Smaller kindreds, with only 1 or 2 affected first-degree relatives, seem to be the rule. This evidence could reflect reduced penetrance or be a result of disease morbidity in utero and prior to reproductive years. Larger kindreds suitable for gene mapping and cloning do exist, but these may represent only specific causal forms of ARVC.
Fig. 1. Clinical findings in ARVC. (A) A T1-weighted spin-echo image of the RV. The myocardium is extensively infiltrated with areas of bright signal suggestive of fat. (B) Identical to A but now, in addition, a chemical fat saturation prepulse has been applied. The areas of signal hyperenhancement on the first image are clearly suppressed on the fat-saturated image, confirming that the RV free wall myocardium is infiltrated with fat extending into the anterior interventricular groove. (C) A typical 12-lead ECG with repolarization abnormalities in the right precordial leads (V₂–V₄). No specific features are present, and the diagnosis of ARVC is completely dependent on the prior probability of this disease or additional abnormalities on other testing. (D) Echocardiographic features of ARVC evident on the apical 4-chamber view demonstrating excessive trabeculations. (E) Echocardiographic features of ARVC evident on the apical 4-chamber view with evidence of an apical aneurysmal segment. (MRI images: Courtesy of Dr David E. Sosnovik and Dr Fred Holmvang, Massachusetts General Hospital; echocardiographic images: Courtesy of Dr Danita M. Yoerger, Massachusetts General Hospital.)
The high rates of familiality support the systematic clinical screening of at-risk relatives.\(^4,28,29\) The identification by screening of presymptomatic individuals or subclinical disease raises many questions regarding their subsequent management.\(^31\) Although these individuals carry the same mutated gene as their relatives with ARVC, the natural history of such forms frustrates the disorder remains to be determined by long-term studies and likely varies widely with the specific causal gene.\(^4,29\) Family studies also may offer insights into the factors modifying progression to clinical disease.

**Molecular Genetics**

Like other highly morbid inherited diseases, ARVC is genetically heterogeneous. There are now 12 genetic loci described for various forms of the disorder, and several unmapped families also are known to exist (Table 1). It is likely that at each locus there will be a high de novo mutation rate and consequent allelic heterogeneity. For these reasons, genetic diagnosis will be subject to many of the technical and interpretive issues already seen with other inherited cardiac syndromes such as hypertrophic cardiomyopathy and long QT syndrome.\(^49\)

The clinical study of extended families suggested a shared pathophysiology between some skin disorders and RV cardiomyopathy. Perhaps the best known of these is Naxos disease, in which palmoplantar keratoderma, woolly hair, and ARVC cosegregate as a recessive syndrome.\(^5\) Similar recessive cardiocutaneous syndromes have been described in other consanguineous populations.\(^50\) Distinct epithelial defects including anterior polar cataracts also have been described in association with ARVC.\(^48\)

These clinical clues led to the identification of a recessive mutation in Naxos disease in the gene encoding plakoglobin, a desmosomal structural protein.\(^5,6\) In turn, this insight led to the detection of homozygous mutations in the desmplakin gene in an Ecuadorian family with recessive biventricular dilated cardiomyopathy, keratoderma, and woolly hair.\(^13,50\) Subsequently, distinct mutations of the desmplakin gene have been found to cause autosomal dominant forms of ARVC (such as ARVC8) and arrhythmogenic LV cardiomyopathy.\(^14,15\) Recently, an autosomal dominant mutation of plakoglobin in a patient with ARVC has also been identified.\(^7\)

Taken together, mutations in plakoglobin and desmplakin represent only a small proportion of ARVC. However, the recent description of plakophilin 2 (PKP2) mutations in a large proportion (25%–70%) of probands with ARVC suggests that this is a major disease locus and underscores the unique role of desmosomal biology in this syndrome.\(^8–10\) Screening of 120 human probands revealed a range of mutations (largely truncations) in 32 individuals.\(^8\) Mutation-positive subjects exhibited similar clinical features as the remaining cohort. The genetic analysis of 2 larger families in the study revealed markedly reduced penetrance, supporting previous clinical reports in ARVC.\(^3\) Subsequent studies screening PKP2 have found mutations in up to 70% of ARVC cohorts with a preponderance of familial cases.\(^9\) These efforts have led investigators to begin systematic screenings of the genes for many desmosomal proteins, and mutations have been identified in desmoglein 2 and desmocollin 2.\(^11,12,16,17\)

Potential mutations have also been reported in the regulatory region of the transforming growth factor \(\beta3\) gene,\(^38\) but the pathogenicity of such mutations is difficult to establish, and confirmatory evidence is awaited. Mutations in the cardiac ryanodine receptor gene (RYR2) have also been described in a single kindred.\(^40,41\) Mutations in the calcium release pathway previously have been associated with catecholaminergic ventricular tachycardia (VT), and it is unclear whether the affected individuals in this family shared such clinical features or exhibited evidence of more typical ARVC.

Potential overlap between ARVC and other clinical entities may be addressed by clinical and molecular genetic studies. For example, because end-stage ARVC is often indistinguishable from dilated cardiomyopathy, only the clinical study of relatives may reveal classic isolated RV involvement. The existence of desmoplakin-related arrhythmogenic left ventricular cardiomyopathy serves to emphasize the limits of clinical classifications.\(^15\) Furthermore, PKP2 mutations do not appear to cause right ventricular outflow tract (RVOT), strongly supporting clinical and electrophysiologic evidence that this entity is distinct from ARVC (L. Thierfelder, unpublished data, 2009). Ultimately, a comprehensive molecular nosology for myocardial disease will resolve many of the inconsistencies in the current classification.\(^51\)

**Disease Mechanisms**

Desmosomes are protein-rich plaques that form mechanically robust connections between cells and serve to organize other key intercellular junctions, including adherens junctions and gap junctions (Fig. 2).\(^52,53\) Although their role in the structural integrity of epithelia and other tissues
<table>
<thead>
<tr>
<th>Locus Name</th>
<th>OMIM #</th>
<th>Genetic Locus</th>
<th>Causative Gene</th>
<th>Mode of Inheritance</th>
<th>Comments</th>
<th>References</th>
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<tbody>
<tr>
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<td>Transforming growth factor β3</td>
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<td>2q32</td>
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<td>3p25</td>
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<td>Founder mutation in large Newfoundland population</td>
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<td>609160</td>
<td>10q22</td>
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<td>AD</td>
<td>? Distinct from DCM</td>
<td>47</td>
</tr>
<tr>
<td>ARVD8</td>
<td>607450</td>
<td>6p24</td>
<td>Desmoplakin (DSP)</td>
<td>AD</td>
<td>Highly pleiotropic Occasionally LV cardiomyopathy only</td>
<td>14,15</td>
</tr>
<tr>
<td>ARVD9</td>
<td>609040</td>
<td>12p11</td>
<td>PKP2</td>
<td>AD</td>
<td>Present in 25% of cases</td>
<td>8–10</td>
</tr>
<tr>
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<td>610193</td>
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<td>Desmoglein 2</td>
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<td>Desmocollin 2</td>
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<td>11,12</td>
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<td>ARVD12</td>
<td>611528</td>
<td>17q21</td>
<td>Plakoglobin (JUP)</td>
<td>AD</td>
<td>Single case with nonsyndromic ARVC</td>
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<td>Palmoplantar keratoderma and wooly hair</td>
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<td>Anterior polar cataract</td>
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Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; OMIM, online Mendelian inheritance in man; ?, significant questions re statements.
has been well defined, other aspects of desmosomal function, including putative roles in cell-cell signaling and intracellular calcium handling, are now being explored. How disruption of these cell junctions by mutant proteins leads to cutaneous or myocardial disease remains unknown.

Perturbed passive mechanical properties and remodeling of the intercalated disc have been documented, but these alone are unlikely to be the sole explanations of the unique susceptibility of the RV in desmosomal disorders. Effects on myocyte differentiation and the development of the RV have been invoked, but experimental support is limited. Mice with a cardiac-specific deletion of desmoplakin recreate many of the pathologic features of ARVC. This work also demonstrated that the perturbation of the Wnt/β-catenin pathway in these hearts was sufficient to push the myocar-dial cells toward an adipocyte cell fate and away from a myocardial cell fate. These data suggest that several steps in RV development and differentiation are likely to be disrupted in ARVC. Spontaneous large animal models of ARVC may prove useful if molecular parallels with human disease are proven, but understanding the entire pathophysiologic process may require the creation of genetically faithful knock-in mouse models.

**DIAGNOSIS**

The intrinsic difficulties in making a definitive diagnosis in ARVC are evident from the existence of the Task Force criteria. Many of the management problems stem from overdiagnosis of isolated individuals with incidental findings or underdiagnosis of relatives of individuals with a clear history of ARVC or sudden death. The most helpful approach to diagnosis is prefaced by an initial estimate of the prior probability of ARVC in any given individual (Fig. 3). This estimate must be based on a careful consideration of the patient’s history of syncope or palpitations, documented arrhythmias, and a rigorous family history. When weighting the family history, it is important to bear in mind the extent of the available information; for example, the absence of a history of sudden death is unhelpful in the face of a limited number of at-risk relatives. Difficult cases are best managed in centers with extensive expertise in the diagnosis and management of ARVC, ideally with systematic evaluation of the entire family.

**Electrocardiography**

Electrocardiography (ECG) may be useful in making the diagnosis of ARVC, but only in the appropriate clinical context (see Fig. 1C). The classic finding of an epsilon wave in the right-sided precordial leads occurred in 20% to 40% of subjects with definitive ARVC, but rarely in other disorders. ECG findings such as T-wave inversion or prolonged S waves in precordial leads V1 to V3 may help discriminate between ARVC and RVOT but are not specific in the general context.
population. Some investigators have seen substantial progression in QRS duration in most of subjects over follow-up periods of 1 to 10 years, but others have seen no ECG progression over several years. Holter monitoring studies consistently identify high rates of ectopy arising from the RV, but here also, specificity is context dependent. Sinoatrial disease and atrial fibrillation are not uncommon. The application of the signal-averaged ECG (SAECG) was expected to improve the sensitivity of noninvasive detection of RV disease, and this has been confirmed by several studies. The use of total filtered QRS (fQRS) duration is sensitive in general as a marker of myocardial disease with several studies suggesting detection rates of more than 90%. In ARVC cohorts, the fQRS duration is predictive of inducible VT at EPS. However, the specificity of SAECG for ARVC depends on the prior probability of disease, and the technique is most likely to be useful in the cases of family members of those already...

**Fig. 3.** A simplified management algorithm for commonly encountered presentations of ARVC.
definitively diagnosed. Other forms of ECG analysis such as measures of QT dispersion have failed to generate reproducible results.

**Echocardiography**

Echocardiographic findings reported in definitive ARVC cases include RV dilation, reduced RV ejection fraction, and focal right ventricular aneurysms. Recent work paying particular attention to the acquisition of RV images revealed that most ARVC patients have some identifiable echocardiographic abnormality. Only 35% of subjects had normal RV function, and most of these were found to have a focal-wall motion abnormality or morphologic abnormality (see Fig. 1D and E). The principal observation from this study was that RVOT enlargement (defined as a diastolic RVOT dimension of 30 mm or greater in the long-axis view) was a reproducible echocardiographic index of RV dilation. It remains to be seen whether such findings discriminate between ARVC and RVOT, and their specificity in unselected cohorts remains unknown. Correlation with other techniques in validated ARVC patients and broader population studies are required to place these data in perspective. Echocardiographic assessment in ARVC requires considerable expertise given the complex 3-dimensional geometry of the RV, the lack of standard reference views, and the load dependence of RV function.

**Magnetic Resonance Imaging**

MRI enables tomographic imaging of the entire RV and combines functional data with tissue characterization capable of detecting fibrofatty replacement of the myocardium (see Fig. 1A and B). Although initial studies were encouraging, overdependence on this technique in the diagnosis of ARVC and the widespread application of cardiac MRI outside of specialized centers with consequent reduced specificity and sensitivity have led to its reappraisal. MRI data from larger populations confirm that intramyocardial fat is seen in substantial numbers of normal individuals. In addition, there are cases of documented ARVC in which the fibrofatty infiltration was not detected by antemortem imaging. More recent work suggests that late enhancement with gadolinium may improve the detection of intramural fibrous regions. Several studies suggest that RV size and function may be more reproducible than the presence or absence of myocardial fibrofatty infiltration, but interobserver variability remains a major issue. However, most of the current approaches have been tested only in small cohorts, and it requires considerable effort to derive rigorous quantitative end points that can reliably discriminate ARVC from other RV pathology or from normal cases.

**Computed Tomographic Imaging**

There is little experience with the use of computed tomographic (CT) scanning in ARVC, but more recent electron-beam multislice scanners may offer a reasonable alternative in cases where MRI is not feasible. Current protocols are able to detect intramyocardial fat, define structural anomalies, and quantitate RV size and function. However, there are few data on the sensitivity or specificity of CT scanning for the diagnosis of ARVC.

**Electrophysiology Study**

The electrophysiologic evaluation of small series of individuals with an LBBB-morphology VT suggests that it may be possible to discriminate successfully between those with ARVC and benign RVOT. Subjects with ARVC were much more likely to have a reentrant tachycardia than those with RVOT who predominantly exhibited automatic tachycardias. In addition, subjects with ARVC were more likely to exhibit fragmented diastolic potentials, multiple inducible tachycardias, a lower success rate for ablation, and lower long-term success rates. Electroanatomic mapping of affected regions in subjects with ARVC revealed lower unipolar amplitudes and a prolonged electrocardiographic duration compared with RVOT subjects or healthy controls. The judicious use of invasive electrophysiologic studies may be helpful in the evaluation of intermediate phenotypes (see Fig. 3).

**Cardiac Catheterization and RV Biopsy**

The role of cardiac catheterization in the diagnosis or management of subjects with ARVC is limited. Individuals may undergo a cardiac catheterization to rule out occlusive coronary disease or to permit the evaluation of RV and LV function, but this is institution dependent. Investigators have identified subjective abnormalities of the RV in many individuals, including deep fissures in the anterior wall, moderator bands, apical aneurysms, and outflow tract dilation. Objective findings in support of the diagnosis of ARVC are uncommon. Endomyocardial biopsy has not been widely used in ARVC, largely because of concern about sampling errors in a regional disease and the risks of free-wall biopsy. Several small studies have suggested that biopsy may be safe and a useful adjunct to noninvasive studies. The greatest
utility may be to identify other suspected causes of RV pathology.\textsuperscript{83}

**Genetic Testing**

The identification of PKP2 mutations in up to 70\% of selected cases suggests that defects in this gene may be a common cause of ARVC.\textsuperscript{8–10} At present, there is no rationale for genetic testing outside of active research protocols, but as the causes of other forms of ARVC emerge and prognostic data accrue for these various entities, this may change. Deriving meaningful prognostic data from the small numbers of ARVC patients remains a challenge, and these difficulties are compounded by genetic and allelic heterogeneity.\textsuperscript{49} These issues emphasize the need for the referral of probands and families to tertiary care centers with active genetic research programs, and the systematic collection of clinical data across the entire spectrum of idiopathic RV disease in large multicenter registries.\textsuperscript{22}

**DIFFERENTIAL DIAGNOSIS**

Several other known conditions may exhibit some of the clinical features of ARVC and confound the diagnosis (Table 2). These disorders are associated with a spectrum of structural and functional involvement of the RV.

Idiopathic VT arising in the RV outflow tract is increasingly recognized as a benign form of arrhythmia occurring in the absence of any detectable structural heart disease. RVOT tachycardias are usually responsive to ß-blockade, and at electrophysiology study (EPS), they are characteristically automatic in nature and amenable to ablation.\textsuperscript{85,86} There is imaging, electrophysiologic and genetic evidence that ARVC and RVOT tachycardia are distinct processes.\textsuperscript{76,85,87} Automatic RVOT tachycardia may be caused by somatic myocardial mutations in some cases,\textsuperscript{88} but they do not appear to be associated with mutations in desmosomal genes.

Uhl anomaly classically presents as a completely atrophic RV, with little or no contractile tissue and functional tricuspid atresia in the neonatal period. Nevertheless, adult presentations have been described, occasionally with ventricular arrhythmias, but more often with intractable RV failure.\textsuperscript{89} The distinction between Uhl and extreme forms of ARVC may not be possible even at autopsy. Multiple cases of Uhls have been reported on fetal echocardiography in single sibships, raising the possibility of a genetic basis.\textsuperscript{80}

Perhaps the largest group of disorders within the differential diagnosis may be other right ventricular cardiomyopathies. Whether some of these represent distinct disease processes or simply milder variants of ARVC is unclear. Subtle forms of Ebstein anomaly, right ventricular noncompaction, or focal RV involvement with inflammatory disorders such as sarcoidosis, or even isolated RV infarction are among other reported confounders.\textsuperscript{31,59,83} Disproportionate abnormalities of RV function are also seen in human immunodeficiency virus patients. Ultimately, the relationships between ARVC and other RV processes may be clarified by genetic techniques.

End-stage forms of ARVC are clinically indistinguishable from other forms of idiopathic biventricular failure. At present, the only convincing method of discriminating between ARVC and dilated cardiomyopathy is direct screening of the extended family to detect less advanced forms

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<th>Table 2</th>
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<td>Differential diagnosis in ARVC</td>
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<td><strong>Diagnosis</strong></td>
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| Right ventricular outflow tract tachycardia | Imaging
Electrophysiology study |
| Uhl anomaly | Unknown |
| Idiopathic dilated cardiomyopathy | Evaluation of extended family |
| Focal RV myocarditis | RV biopsy |
| HIV-induced cardiomyopathy | Clinical context |
| Isolated RV infarction | Coronary angiography |
| Ebstein anomaly | Imaging
Electrophysiology study |
| Sarcoidosis | RV biopsy |
| Carcinoid | Clinical context |
of ARVC in relatives. Genetic testing eventually may be able to perform these diagnostic and screening functions. Although left ventricular hypertrophy is seen in autopsy series of ARVC, it is not widely reported in clinical studies, and discrimination from hypertrophic cardiomyopathy is not a common problem.

Clinical Management

The management of ARVC is focused largely on the prevention of sudden death. In those who experience syncopal events or have symptomatic VT or have survived a cardiac arrest, the appropriate interventions are obvious. However, an increasing number of individuals have some features of ARVC, but its correct diagnosis and management in them remain unclear. It is unlikely that rigorous, controlled data will become available for most interventions in ARVC; therefore, therapeutic decisions are driven by sensible extrapolation from related clinical settings. Until more rigorous data are available, the approach to ARVC is best viewed within the context of the Task Force criteria while highlighting necessary qualifiers and the overall limitations of this strategy (see Fig. 3 and Table 2).

Antiarrhythmic Medications

Because most definitive ARVC cases are now treated with implantable cardioverter defibrillators (ICDs), pharmacologic antiarrhythmic therapy is typically adjunctive. In the absence of severe RV contractile dysfunction, β-blockers are well tolerated. The class III agent sotalol, which also exhibits some β antagonism, has emerged as a first-line therapy. Amiodarone is a second line agent in patients with refractory ventricular arrhythmias.

Implantable Cardioverter Defibrillator

With the expanding indications for ICD use, prophylactic ICD implantation in definitive cases of ARVC has become the mainstay of therapy. Randomized controlled trials are not feasible in such a rare and heterogeneous syndrome, but observational studies confirm that defibrillators are effective in preventing sudden death in high-risk cohorts. The most extensive series consisted of 132 patients, and more than 70% of them presented with a ventricular fibrillation arrest or sustained VT. During a mean follow-up of 39 months, nearly one-half of the patients had an appropriate therapy, 16% had an inappropriate therapy, and 14% had a device-related complication. ICD implantation in affected members of high-risk families confirms these findings.

In cohorts with a lower incidence of aborted sudden cardiac death or unstable VT on presentation, the risk-benefit ratio may still favor an ICD. The induction of LBBB morphology VT on a preimplantation EPS may predict appropriate ICD therapy. Similar outcomes were observed in several other smaller studies. There may be a high rate of arrhythmia storm in this population, raising the possibility that sudden death is a result of an additional process, such as inflammation, superimposed on the basal ARVC substrate.

Increasingly, ICDs are implanted in individuals with little evidence of an elevated risk of sudden death.

Catheter Ablation

The VTs observed in patients with ARVC are amenable to entrainment mapping similar to more common scar-mediated ventricular arrhythmias. Typical patients exhibit multiple inducible VTs, as expected in a diffuse cardiomyopathy. Nevertheless, ablation is successful in approximately 50% of the cases, suggesting that it may play a useful palliative role in the management of recurrent arrhythmias.

Heart Failure Therapies

The precise incidence of heart failure in ARVC is unknown and probably varies widely with the specific underlying cause. The high frequency of RV hypokinesis, RV aneurysms, and regional wall motion abnormalities in ARVC suggests that formal anticoagulation might have a role to play. There are reports of pulmonary or systemic embolism in ARVC; however, these are study specific. Angiotensin-converting enzyme inhibitors, or other vasodilators if these are contraindicated, seem reasonable if there is clinical evidence of heart failure, particularly in the presence of LV dysfunction. Cardiac transplantation is unusual in ARVC but has been performed for incessant VT and end-stage contractile failure. It is possible that with the prevention of sudden death by ICD, ventricular dysfunction in later stages of ARVC will be uncovered.

Exercise Recommendations

Several smaller series have suggested a role for adrenergic drive or exercise in the precipitation of fatal arrhythmias. However, the only large unsellected series found that almost all sudden deaths occurred during normal daily activities. Nevertheless, it may be reasonable to recommend the avoidance of strenuous activity.
Screening of Relatives

ARVC is frequently an inherited disease, exhibits reduced penetrance, and may present with sudden death. These observations, combined with the apparent success of the ICD therapy, predicate the directed screening of asymptomatic, at-risk (that is, at risk for having inherited the same genetic defect) family members. In the context of a probability of up to .50 that a given relative has inherited the gene defect causing ARVC in the proband, even minor cardiac abnormalities well below the threshold set by the Task Force guidelines take on great significance. In view of the reduced penetrance observed in most families, screening should be extended throughout the kindred to at least one generation beyond the last affected individual. In ARVC, as in other Mendelian forms of cardiomyopathy, the implications of subtle clinical findings often are only interpretable in the context of data from the entire extended family.3 For this reason, such assessments are best undertaken at tertiary centers with a special interest in inherited forms of sudden death. Legislated investigation of unexplained sudden death by specialist teams is under evaluation in some countries.

Asymptomatic family members with a normal comprehensive evaluation are less likely to have inherited the gene defect, but should undergo follow-up at regular intervals (every 2–3 years) until definitive diagnostic tools are available. In the context of a proband with confirmed disease, family members with subtle signs of ARVC but no symptoms almost certainly are affected, but their risk of progressing to develop clinical problems is difficult to define. At present, decisions regarding ICD implantation in relatives are best undertaken in specialized centers with expertise in the management and counseling of families with ARVC. Until the different disease entities underlying ARVC are understood and robust clinical or molecular prognostic tools are available, decisions on prophylactic ICD placement should be circumspect.

FUTURE STUDIES AND SUMMARY

A central goal of future studies must be the systematic collection of unbiased cohorts not only of individuals who meet Task Force criteria, but also the relatives of probands with definitive ARVC and other individuals in whom the diagnosis is being considered. When combined with proband-based clinical and molecular genetic studies, such systematic data collection allows the prospective testing and weighting of any proposed diagnostic criteria. Wherever possible, the development of reproducible quantitative indexes of RV structure and function facilitates comparisons between cohorts and the normal population. Efforts to develop novel diagnostic modalities, including biomarkers, molecular imaging, and genetic testing are under way, and innovative approaches exploiting the pathophysiologic links with other tissues such as skin could be productive.

The identification of the causal mutations in different forms of ARVC may enable the discrimination of gene-specific features. Because the causal genes are so mechanistically faithful, animal models will become feasible. It is important to explore the pathways by which desmosomal dysfunction results in the perturbation of normal myocardial differentiation and ultimately leads to RV cardiomyopathy and arrhythmias. Understanding the basis of RV development and the unique features of RV structure and function assists the dissection of disease mechanisms and sheds light on potential therapies and prevention.

REFERENCES

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