Arrhythmogenic Cardiomyopathy

Left-Dominant Arrhythmogenic Cardiomyopathy
An Under-Recognized Clinical Entity

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Objectives
We sought to investigate the clinical-genetic profile of left-dominant arrhythmogenic cardiomyopathy (LDAC).

Background
In the absence of coronary disease and left ventricular (LV) systolic dysfunction, lateral T-wave inversion and arrhythmia of LV origin are often considered benign. Similarly, chest pain with enzyme release might be attributed to viral myocarditis. We hypothesized that these abnormalities might be manifestations of the “left-dominant” subtype of arrhythmogenic right ventricular cardiomyopathy.

Methods
The 42-patient cohort was established through clinical evaluation of individuals with unexplained (infero)lateral T-wave inversion, arrhythmia of LV origin, and/or proven LDAC/idiopathic myocardial fibrosis in the family.

Results
Patients presented from adolescence to age >80 years with arrhythmia or chest pain but not heart failure. Desmosomal mutations were identified in 8 of 24 families (15 of 33 patients). Magnetic resonance findings included LV late-enhancement in a subepicardial/midwall distribution, corresponding to fibrofatty replacement and fibrosis on histopathology. Fifty percent had previously been misdiagnosed with viral myocarditis, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, or idiopathic ventricular tachycardia. Arrhythmic events included presentation with ventricular fibrillatory arrest in 1 patient and 2 instances of sudden cardiac death during follow-up.

Conclusions
Arrhythmogenic cardiomyopathy is distinguished from DCM by a propensity towards arrhythmia exceeding the degree of ventricular dysfunction. The left-dominant subtype is under-recognized owing to misattribution to other disorders and lack of specific diagnostic criteria. Clinicians are alerted to the possibility of LDAC in patients of any age with unexplained arrhythmia of LV origin, (infero)lateral T-wave inversion, apparent DCM (with arrhythmic presentation), or myocarditis (chest pain and enzyme rise with unobstructed coronary arteries). (J Am Coll Cardiol 2008;52:2175–87) © 2008 by the American College of Cardiology Foundation

Left-dominant arrhythmogenic cardiomyopathy (LDAC) is characterized pathologically by fibroadipose replacement of the left ventricle (LV), often occurring as a circumferential band in the outer one-third of the myocardium and the right side of the interventricular septum (1–4). First described at post-mortem examination in sudden cardiac death (SCD) victims, LDAC has been observed in vivo in surviving relatives, patients with ventricular tachycardia (VT) of LV origin, and families with desmoplakin mutations (5–9).

More recently, LDAC has been recognized as 1 of 3 patterns of disease expression among families with arrhythmogenic right ventricular cardiomyopathy (ARVC) (10). In contrast to the “classic” subtype, with its well-known predilection for the right ventricle, and the “biventricular” variant, defined by parallel involvement of both ventricles, LDAC is characterized by early and predominant LV involvement (10). Salient features include inverted T waves in the lateral and/or inferior leads and ventricular arrhythmia of right bundle branch block (RBBB) morphology, consistent with LV origin (1,5–7,10). In everyday clinical
practice, these abnormalities are often considered benign in the absence of obstructive coronary artery disease and LV systolic dysfunction.

Less well-defined is the entity known as idiopathic myocardial fibrosis (IMF), which accounts for 1% to 3% of cases of SCD (11–13). Idiopathic myocardial fibrosis is characterized by heterogeneous interstitial fibrosis with a predilection for the inferior LV wall (13). Replacement fibrosis is also observed; however, coronary artery disease and other structural abnormalities are by definition absent, indicating a repair process for which the primary insult is unknown. While infectious myocarditis and age-related degeneration have been cited as possible causes, it has also been suggested that IMF might be part of the same disease spectrum as ARVC. The clinical counterpart of IMF remains incompletely understood.

Although the relative paucity of clinical reports of LDAC and IMF is anecdotally attributed to their low prevalence, underrecognition might be a factor. We sought to define the clinical and genetic profile of LDAC/IMF and facilitate incorporation of its features into forthcoming revisions of the task force diagnostic criteria for ARVC.

**Methods**

The Heart Hospital is a tertiary center with a dedicated Inherited Cardiovascular Disease service. Standard referrals include index cases with established or suspected hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or ARVC and relatives requiring prospective assessment for familial cardiomyopathy or sudden unexplained death syndrome. All patients are evaluated de novo to provide independent diagnosis and plan management strategies.

The study protocol is outlined in Table 1 (14–18), including inclusion/exclusion criteria at each stage and details of clinical work-up and genetic studies. During stage 1, we identified a series of patients with arrhythmia of LV origin or (infero)lateral T-wave inversion in whom reassessment failed to confirm the referring diagnosis. These individuals were entered into the study on the basis of unexplained ventricular arrhythmia of RBBB morphology and/or inverted T waves in the LV leads. Individuals with proven LDAC/IMF in the family comprised the remainder of the initial study population. In stage 2, probands with structural features of arrhythmogenic cardiomyopathy and relatives with left-sided features (viz., arrhythmia of LV origin, inverted T waves confined to the [infero]lateral leads, predominant LV dilatation/dysfunction, or marked late gadolinium enhancement [LGE] in the LV with preserved right ventricular [RV] function) were entered into the final LDAC cohort to allow proposal and validation of clinical diagnostic criteria.

**Statistical analysis.** Data were tested for normality with the Shapiro–Wilk test. The Spearman and Pearson correlation coefficients were calculated as appropriate. Two-tailed p values are cited to 4 decimal places. Key percentages are provided with 95% confidence intervals (CIs).

**Results**

**Initial study population.** The initial study population comprised 73 individuals from 29 different families. During the 4-year study period, only 2 patients were referred for evaluation of VT of presumed LV origin with cause unknown. A further 17 patients had been referred with difficult-to-manage arrhythmia or challenging risk stratification issues in the setting of a presumed diagnosis of DCM (n = 12), HCM (n = 3), mitral valve prolapse (n = 1), or myocarditis/left ventricular noncompaction (LVNC) (n = 1). The patients with presumed HCM did not fulfill the diagnostic criteria thereof. The diagnosis was queried in the patients with presumed DCM owing to presentation with symptoms of arrhythmia, historic and contemporary absence of clinical heart failure, and burden of ventricular arrhythmia out of proportion to the often mild degree of LV dilatation/dysfunction. At initial review, all 19 patients were considered to have otherwise unexplained arrhythmia of LV origin and/or (infero)lateral T-wave inversion and were entered into the study on this basis. In 6 patients, the indication for referral was a family history of DCM (n = 3), ARVC (n = 2), or sudden unexplained death syndrome (n = 1), but enrollment into the LDAC study was based on identification of unexplained arrhythmia of LV origin and/or inverted T waves in the LV leads. The remaining 48 patients were recruited on the basis of proven LDAC (n = 43) or IMF (n = 5) in the family; of these, 4 had previously presented to local centers and been diagnosed with myocarditis/idiopathic VT (n = 2) or benign ventricular ectopy (n = 2).

**LDAC cohort.** Twenty subjects with a family history of LDAC/IMF had no abnormalities on clinical evaluation and were not eligible for stage 2. A further 11 individuals
from 5 different families had evidence of arrhythmogenic cardiomyopathy but demonstrated “classic” RV or “biventricular” disease expression and were excluded from the LDAC cohort owing to a lack of “left-dominant” features. The remaining 42 patients were entered into the final LDAC cohort.

Demographic data, electrocardiography, and arrhythmic findings. Baseline clinical characteristics of the LDAC cohort are presented in Table 2. Of 29 patients aged ≥40 years, 19 (66%) had previously undergone cardiac catheterization, which showed unobstructed coronary arteries in all cases. Three of these patients had been hospitalized with...
Structural abnormalities on CMR/echocardiography: LVEDV, % predicted (range) 127 ± 25 (83–186); LVEDV above upper limit of normal 24 (59%; 95% CI 42–73%); LVEF (%) 54 ± 11; LVEF < 55% 23 (56%); LVEF < 55% with normal LVEDV 8 (20%); RVEDV (n = 32) 124 ± 29; RVEDV above upper limit of normal 11 (27%; 95% CI 15–43%); RVEF (%) 53 ± 7; LV wall motion abnormalities 25 (61%); Septum 16 (39%); Apex 21 (50%); Inferior wall 7 (17%); Inferolateral wall 8 (20%); Anterolateral wall 6 (15%); Anterior wall 3 (7%); RV regional dilation/wall motion abnormalities 36 (86%); Right ventricular outflow tract 30 (73%); Subtricuspid 33 (80%); Mid-free wall 30 (73%); Distal free wall 9 (22%); Apex 14 (34%).

Exercise testing with metabolic gas exchange measurements (n = 32) Peak oxygen consumption, ml/kg/min 25.5 ± 9.1; Peak oxygen consumption, (range) 84.3 ± 20.9 (51–151).

Tissue characterization by CMR: Late enhancement in LV 40/40 (100%; 95% CI 89–100%).

<table>
<thead>
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N = 42. *One patient presented with ventricular fibrillation (VF) arrest. †CMR was performed in 41 of 42 patients. The exception died suddenly at her local hospital while awaiting inpatient transfer for further investigations. One boy did not receive gadolinium-diethyltriaminepentaacetic acid due to age and weight stipulations. ‡Thirty-four patients (81%) had ventricular arrhythmia of grade ≥ 2. Ventricular extrasystoles were recorded in sufficient leads, predominantly during exercise testing, to permit analysis of morphology in 33. Of these, 23 (68%) had ventricular arrhythmia of RBBB morphology only, consistent with LV origin. The remaining 18 (55%) had PVCs of both RBBB and left bundle branch block configuration. §The prevalence of RV late enhancement is not cited, owing to the difficulty of distinguishing this feature from myocardial fat, compounded by setting of inversion times to null the LV myocardium and the absence of a fat-suppressed inversion recovery sequence. EF = ejection fraction; SAE CG = signal-averaged electrocardiogram; SCD = sudden cardiac death; other abbreviations as in Table 1.

Continued
Table 3  Summary of Desmosomal Gene Changes Isolated in LDAC Cohort

<table>
<thead>
<tr>
<th>Gene</th>
<th>Nucleotide Change</th>
<th>Predicted Effect</th>
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<th>Comment</th>
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</thead>
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<tr>
<td>DSP</td>
<td>3337T→G</td>
<td>Nonsense; premature termination (R1113X)</td>
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<td>Family A</td>
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<td>DSP</td>
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<td>In highly conserved amino acid region (N-terminal)</td>
</tr>
<tr>
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<td>1520C→T</td>
<td>Missense (S507F)</td>
<td>2</td>
<td>In highly conserved amino acid region (N-terminal)</td>
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<tr>
<td>DSP</td>
<td>1755insA</td>
<td>Frameshift; premature termination (T586fsX594)</td>
<td>4</td>
<td>Family D</td>
</tr>
<tr>
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<td>999 + 1G→A</td>
<td>Mutant splice product; premature termination</td>
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<td>Previously published* (2034insA)</td>
</tr>
<tr>
<td>PKP-2</td>
<td>419C→T</td>
<td>Missense (S140F)</td>
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<td>DSG-2</td>
<td>1773_1774delTG</td>
<td>Frameshift; premature termination C591X</td>
<td>1</td>
<td>Extracellular anchor domain (previously published)*</td>
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</tbody>
</table>

*The C591X mutation in desmoglein-2 (DSG-2); S140F mutation in plakophilin-2 (PKP-2); and the desmoplakin mutations identified in families D and E have been previously reported within the context of gene identification studies (data from references [7,16,20,21]).

DSP = desmoplakin.

dicted, 12 had left ventricular ejection fraction (LVEF) <50%, and 2 had LVEF <35%. In comparison, the maximum LV end-diastolic dimension determined by echocardiography was 6.1 cm, whereas the lowest LVEF was 40%. Five patients (13%) had LVEF <50% without marked enlargement of LVEDV (<120% predicted).

Five subjects fulfilled the Chin and Jenni criteria for LVNC (19). Two had histological evidence of fibrofatty replacement on endomyocardial biopsy and were found to carry desmosomal gene mutations (Table 3). Of the remaining 3 patients, 1 had a family history of pathologically proven ARVC and 1 was Afro-Caribbean, noteworthy because 13% of normal Afro-Caribbean control subjects in a recent series fulfilled criteria for noncompaction (19). The third suffered SCD during follow-up with post-mortem findings of IMF (Table 4). Affected relatives had clinical evidence of LDAC without features of LVNC.

LV LGE was frequently present in a segment without coincident wall motion abnormality (WMA) (76 of 107 [71%] of affected segments). Circumferential LGE, extending through the outer one-third of the LV myocardium to the right side of the septum, was apparent in 10 subjects (24%); others demonstrated a more patchy distribution (Figs. 1A and 1B). Severe LV LGE (LV lesion score = 4) with normal LVEDV was observed in 7 patients, of whom 4 also had preserved global LV systolic function.

Of the 41 LDAC patients who underwent CMR, 36 (88%; 95% CI: 73% to 95%) had segmental dilation and/or WMA in the RV, often localized to the triangle of dysplasia and mid-free wall. RV aneurysms were present in 14 (34%), but only 11 (27%) had RVEF below the lower limit of normal for age and gender. Fourteen patients (34%; 95% CI: 21% to 51%) had LV dilation and/or systolic impairment with normal RV volumes and function. There was no significant correlation of RV/LV volume ratio with age (Spearman r = −0.08). Three patients were exceptional in demonstrating significant RV dilation, with an RV/LV volume ratio ≥1.2. All 3 had initially presented with a high
burden of premature ventricular complexes (PVCs) of RBBB morphology, and 1 also had T-wave inversion in V₄ to V₆, enabling inclusion in the original study population. CMR subsequently revealed regional disease (RV WMA in 2, LV WMA and RV aneurysms in the other) and LV LGE consistent with arrhythmogenic cardiomyopathy, allowing entry into the LDAC cohort. However, the combination of left-sided features (arrhythmia of LV origin, extensive LV LGE, ± lateral T-wave inversion) with RV dilation was recognized to be more in keeping with the “biventricular” subtype of arrhythmogenic cardiomyopathy than LDAC. Excluding these 3 individuals, the mean RV/LV volume ratio was <1 (0.97 ± 0.15).

**Clinical correlations.** The LVEDV, expressed as a percentage of predicted, correlated with arrhythmia score (r = 0.42, p = 0.0058), but a weaker positive correlation with the LV lesion score (r = 0.29) did not reach statistical significance. There was a weak inverse correlation between LVEF and arrhythmia score (r = −0.36, p = 0.0191). Nevertheless, 7 patients (17%; 95% CI: 8% to 32%) had arrhythmia scores ≥3 with LVEDV <120% of predicted and LVEF ≥50%. The LV lesion score showed inverse correlation with LVEF (r = −0.35, p = 0.0258) and stronger positive correlation with arrhythmia score (r = 0.48, p = 0.0018).

**Short- and medium-term follow-up.** Follow-up data were available in 41 of 42 patients, with duration ranging from 1 to 60 months (mean 42 months). Three events were recorded (Table 4). Nine LDAC patients underwent prophylactic implantable cardioverter-defibrillator placement for syncope (n = 2) and pre-syncope associated with nonsustained VT (n = 6) or multiple instances of SCD in the family (n = 1). Endomyocardial biopsies were obtained at the time of device implantation in 2 patients, 1 of whom had previously been diagnosed with viral myocarditis. Samples from the interventricular septum in both revealed loss of myocytes with fibroadipose replacement. The histological findings were in keeping with the presence of septal LGE on CMR.

**Genetic profile of LDAC cohort.** Results of molecular genetic analysis in the LDAC cohort are shown in Table 3 (7,16,20,21). Disease-causing mutations were identified in 8 of 24 families (15 of 33 individuals), equivalent to a pick-up rate of 33% (95% CI: 16% to 55%). Successfully genotyped individuals included the 4 who had originally presented with acute chest pain and presumed viral myocarditis.
Genotype–phenotype correlations: desmoplakin disease.

Novel mutations in desmoplakin were identified in 2 LDAC families (A to B) (Figs. 2 to 4), the sole affected living first-degree relative of an SCD victim with IMF (family C), and 2 affected relatives of a deceased proband (family D). In all cases, the mutations cosegregated with clinical phenotype (Table 5), with penetrance approaching 100% from late adolescence in families A to B. Absence of the mutation was associated with normal clinical status in all those evaluated.

Prior diagnoses in LDAC patients. The final LDAC cohort included the 17 patients and 4 relatives with alternative diagnoses at referral (DCM, HCM, mitral valve prolapse, myocarditis/LVNC, idiopathic VT, and benign ectopy). Among the 3 patients with presumed HCM, inclusion of a tendon during echocardiographic measurement of the septum had erroneously suggested asymmetric septal hypertrophy in 1; apical trabeculation had been misinterpreted as distal HCM in another. The third had a family history of “cardiomyopathy” that was presumed hypertrophic and was thought to have burnt-out disease, owing to mild LV dilation. Subsequent evaluation of her family was consistent with LDAC in affected members.

Frequent PVCs of RBBB morphology had been attributed to mitral valve prolapse in another patient; contrast echocardiography and CMR demonstrated additional features of RV WMA, myocardial fat, and LV LGE, consistent with arrhythmogenic cardiomyopathy. One 42-year-old woman had been diagnosed with both myocarditis and LVNC for a triad of chest pain, frequent PVCs, and prominent LV trabeculation on imaging. The final diagnosis of LDAC was supported by characteristic findings on endomyocardial biopsy and isolation of a mutation in desmoglein-2 (Table 3).

Discussion

We have previously reported early LV involvement in familial ARVC, supporting adoption of the broader term “arrhythmogenic cardiomyopathy,” with subclassifications to reflect the classic right-sided, biventricular, and left-dominant patterns of disease expression (10). Herein we describe our experience with diagnosis and treatment of
LDAC. Our findings highlight the interrelation of LDAC and ARVC within the same disease spectrum and provide a composite profile of this entity.

**Clinical-genetic-pathological profile of LDAC.** LDAC may present over a wide age range, from adolescence to age >80 years, typically with palpitation and symptoms of impaired consciousness. Physical examination is frequently unremarkable. Ventricular arrhythmia of RBBB morphology is characteristic and often out of proportion to the degree of LV dysfunction. Many patients have an additional arrhythmic focus in the RV. A 12-lead ECG may show left deviation of the QRS axis or inverted T waves in the (infero)lateral leads. Imaging demonstrates regional and/or global LV dysfunction. A key CMR finding is LV LGE in a subepicardial/midmyocardial distribution (Fig. 4). The RV might show WMA (10), dilation, and systolic dysfunction but is affected less severely than the LV. SCD is the major complication, whereas clinical heart failure is rare. One-third of the genotyped LDAC cohort (15 of 33 patients from 8 of 24 families) had causative mutations in desmosomal genes already implicated in ARVC (desmoplakin, plakophilin-2, and desmoglein-2), similar to the current pick-up rate from genotyping in ARVC (22). The genetic affiliation of these entities is further underscored by their frequent coexistence within the same family: the 11 affected relatives excluded from the final cohort had a family history of LDAC/IMF but showed “classic” or “biventricular” disease patterns (10). Findings on histopathology included myocyte loss, fibrofatty replacement, and chronic inflammatory infiltrates, again paralleling the RV changes of ARVC (23,24).

**LGE.** LGE allows determination of the presence, location, and transmural extent of scarring in myocardial infarction, in which it invariably involves the subendocardial layer (25–27). In HCM, LGE is predominantly mid-myocardial, occurs in hypertrophied regions, and is associated with increased myocardial collagen content; its extent is linked with progressive disease and risk factors for SCD (28,29). Midwall LGE has also been observed in patients with DCM, in which it serves as a predictor of VT and SCD and corresponds to macroscopic, midmyocardial fibrosis on post-mortem examination (30).

In ARVC, LGE originally attracted interest for tissue characterization of the RV, where its presence correlates with fibrofatty replacement on endomyocardial biopsy and inducibility of VT during electrophysiological studies (31). Subsequent studies have highlighted the utility of LGE in delineating LV involvement in ARVC. The subepicardial/midmyocardial distribution and predilection for the inferior/inferolateral LV walls show close agreement with patterns of fibrosis in ex vivo hearts from SCD victims and transplant recipients (10,14,23).

In the LDAC cohort, septal LGE was associated with the presence of fibroadipose replacement in the 2 patients who underwent endomyocardial biopsy. Patchy midwall LGE in a patient who subsequently suffered SCD was associated with diffuse interstitial fibrosis on post-mortem examination. LGE may therefore detect both interstitial and reparative fibrosis. A noteworthy finding in 20% of LDAC patients was circumferential LGE, resembling the band of fibrous tissue described by pathologists in LDAC hearts (1–4). The extent of LGE showed strong correlation with arrhythmia score. LV LGE is commonly observed in the absence of coincident WMA and can be extensive without global LV dilation or systolic dysfunction. Both of these factors potentially contribute to under-detection of the structural abnormalities of LDAC by conventional 2D echocardiography.

**IMF.** In 2 probands from our cohort who suffered SCD during follow-up, gross autopsy findings were minimal, but histology revealed interstitial fibrosis consistent with IMF, localized to the inferior and lateral walls in 1 case, and diffuse in the other. We are therefore able, for the first time, to describe the in vivo counterpart of IMF. Both individuals presented with pre-syncopal symptoms and had documented VT of RBBB morphology, with inferior T-wave...
Table 5  Genotype-Phenotype Correlations in Families With Novel Mutations in Desmoplakin

<table>
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<th>Family A (Pedigree, Fig. 2) (3337C→T Mutation in DSP)</th>
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<td><strong>A1</strong> 35/F*</td>
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<td></td>
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<tr>
<td><strong>A3†</strong> 72/M</td>
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<td><strong>A4†</strong> 37/F</td>
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<tr>
<td><strong>B1</strong> 26/F*</td>
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<tr>
<td><strong>B2†</strong> 43/F</td>
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<td></td>
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<tr>
<td><strong>B17</strong> 12/M</td>
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<td><strong>B18</strong> 13/M</td>
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</table>

**Family B (Pedigree, Fig. 2) (3045delG mutation in DSP)**

| **B3** 19/M | Asymptomatic with normal ECG, signal-averaged ECG, echocardiogram, exercise test, and Holter. CMR: RV WMA and midwall septal LGE in 2 discrete regions (Fig. 4).  |
| **B4†** 41/F | Presented locally aged 41 yrs with palpitation, pre-syncopal symptoms, LVEF 30%–40%. Angiographically normal coronary arteries; preliminary diagnosis dilated cardiomyopathy. Standard therapy with angiotensin-converting enzyme inhibitor, diuretic, and low-dose beta-blocker commenced, without symptomatic improvement. Holter monitoring revealed >15,000 multifocal PVCs/24 h, including runs of nonsustained VT.  |
| **B11** | Brief, infrequent episodes of palpitation. Left-axis deviation and lateral T-wave inversion on 12-lead ECG; frequent and complex arrhythmia of biventricular origin. CMR revealed RV aneurysms at subtricuspid region and mid-free wall and WMA at the outflow tract and apex. LV apex dilated and dysskinetic. Extensive LV LGE observed in circumferential pattern (Fig. 4).  |

**Family C (1325C→T mutation in DSP)**

| **C1** 44/M* | Active, athletic proband suffered SCD at rest, apparently without premonitory symptoms. Post-mortem: septal fibrosis without ventricular hypertrophy or dilation. IMF was diagnosis of exclusion.  |
| **C2** 40/F | Sister of proband. In her 20s she had 6-month cyclical flu-like illness that defied diagnosis. Manifestations included fever, diaphoresis, and weight loss but no respiratory symptoms.  |
| **D1** 32/M* | Suffered SCD after dizzy spells and at least 1 syncopal episode. Post-mortem demonstrated arrhythmogenic cardiomyopathy with prominent LV involvement.  |
| **D2** 69/F | Mother of proband. Prior syncopal episodes; current episodic palpitation. 12-lead ECG: inverted T waves in V5 to V6. Frequent PVCs of both LV and RVOT origin. CMR: LV mildly dilated; LVEF 43%; extensive circumferential LV LGE; aneurysms at RVOT and RV subtricuspid region.  |
| **D3** 47/F | Sister of proband. Longstanding history of sustained palpitation at rest (often nocturnal). 12-lead ECG: leftward QRS axis; equivalent R-wave progression; flattened T waves in I, V5 to V6, and inferior leads. Exercise testing: peak oxygen consumption 30.2 ml/kg/min (117% of predicted); multiple PVCs and nonsustained VT of predominantly LV origin observed. CMR revealed localized dilatation and WMA at RVOT and subtricuspid region, with extensive LV LGE including septum.  |

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*Deceased.  †Implantable cardioverter-defibrillator placement.  
MI = myocardial infarction; LVEDD = left ventricular end-diastolic diameter; LVNC = left ventricular non-compaction; RVOT = right ventricular outflow tract; other abbreviations as in Tables 1 and 2.
inversion or left bundle branch block (LBBB) on resting ECG (Table 4). One patient underwent antemortem CMR examination, which revealed extensive patchy midwall LV LGE. Two of his relatives presented independently and showed similar findings.

The clinical profile of IMF therefore overlaps with that of LDAC. Clinical features of ARVC were also observed in 2 families who had lost a first-degree relative to IMF; a desmoplakin mutation was subsequently identified in 1 (C2), suggesting that IMF might be a clinical manifestation of arrhythmogenic cardiomyopathy. A major distinction between the 2 entities has hitherto been the presence of myocardial fat in arrhythmogenic cardiomyopathy. Experience with Carvajal syndrome, however, suggests that fat is not a requisite feature in all forms of arrhythmogenic cardiomyopathy. Carvajal syndrome was originally described as a triad of palmoplantar keratoderma, woolly hair, and DCM secondary to a homozygous mutation in desmoplakin (32). Detailed pathological examination of the heart from a Carvajal patient demonstrated myocardial fat loss and replacement fibrosis in the subepicardial layers, and aneurysms in both the LV and RV triangle of dysplasia. Clinical findings include precordial T-wave inversion and early arrhythmogenicity; the subsequent prevalence of heart failure is a probable corollary of the homozygous mutation, with the gene-dose effect causing rapid progression to end stage disease. Despite the absence of adipose replacement, the phenotype is more typical of arrhythmogenic cardiomyopathy than DCM (32). Fibrofatty replacement likely represents a nonspecific reparative process; why adipose tissue predominates in some patients while others manifest only fibrosis remains unclear.

Also unresolved is the predominance of interstitial fibrosis, as opposed to replacement fibrosis, in some cases of IMF (13). Whereas replacement fibrosis is a repair mechanism after cell loss, interstitial fibrosis is a reactive process that occurs in the absence of myocyte necrosis, in response to triggers as disparate as ventricular hypertrophy, radiation, and ischemia. Both forms of fibrosis have been observed in ARVC (23).

The role of myocarditis. It has recently been suggested that the LDAC phenotype is the result of chronic myocarditis (33), with or without underlying ARVC. Several lines of evidence seem to support this premise. First, almost one-third of the cohort reported recurrent chest pain. Second, 4 patients had a prior diagnosis of myocarditis (presumed viral) on the basis of an episode of acute chest pain in the setting of angiographically normal coronary arteries. Third, both subepicardial and midwall LGE have been reported in patients fulfilling Dallas criteria for myocarditis on endomyocardial biopsy (34) and among individuals with chest pain, Troponin rise, and unobstructed coronary arteries (35). Familial evaluation was not conducted in either population.

In contrast, our study was distinguished by active investigation for familial disease, which was proven in 83% and suspected in a further 12% owing to a family history of premature SCD. Furthermore, 38% of genotyped patients
in the LDAC cohort had mutations in desmosomal genes, strengthening the view that LDAC is an inherited, genetically determined disorder.

The apparently conflicting findings are best reconciled by postulating that inflammatory myocarditis is part of the natural history of arrhythmogenic cardiomyopathy, where it has a genetic rather than an infective basis. Focal lymphocyte infiltrates and myocyte necrosis consistent with myocarditis occur in up to 67% of ARVC hearts on post-mortem examination (24), lending further support to this premise. Bauce et al. (8) described clinical presentation with myocarditis in 2 siblings with familial arrhythmogenic cardiomyopathy secondary to a mutation in desmoplakin. Both had chest pain, ST-segment elevation, and myocardial enzyme release in the setting of angiographically normal coronary arteries.

The desmosomal model of arrhythmogenic cardiomyopathy offers an explanation at a molecular level (9,22). Desmosomes are specialized intercellular junctions that anchor intermediate filaments to the cytoplasmic membrane in adjacent cells, imparting mechanical strength via both cell–cell adhesion and transmission of force between the junctional complex and the cytoskeleton. Mutations in desmosomal genes may compromise either intercellular adhesion or intermediate filament function or both, depending on their impact on protein structure and function. Consequent myocyte loss may be accompanied by an inflammatory response and is followed by repair with fibrous or fibrofatty tissue. Rather than being a continuous process, disease progression is purported to occur during occasional “hot phases” (22), when an unknown stimulus activates cell loss and inflammation in a previously quiescent region of the myocardium. Therefore a proportion of adults with chest pain, unobstructed coronary arteries, and apparent myocarditis might have underlying arrhythmogenic cardiomyopathy.

Activation of the disease process might also result in transient electrical instability and rarely SCD. Should death occur during an early “hot phase,” post-mortem examination of the heart might show myocyte necrosis and inflammatory infiltrates in lieu of the characteristic fibrofatty replacement, as in case B1 (Table 5) and as previously described by Bauce et al. (8).

**LDAC versus ARVC with LV involvement.** LV involvement in the advanced stages of ARVC is well recognized (8,23). In light of the high prevalence of RV abnormalities, it is tempting to ascribe the LDAC phenotype to normal disease progression. There are, however, several counters to this premise. First, over 75% of LDAC patients had ventricular arrhythmia of RBBB morphology, although just over one-half had an additional LBBB-type focus. “Classic” ARVC is characterized by ventricular arrhythmia of LBBB morphology, as outlined in the task force criteria for ARVC; multifocal arrhythmia is less frequently reported, and pure LV arrhythmia occurs very seldom. Second, the most common ECG finding was T-wave inversion confined to the (infero)lateral leads; gradual extension to the right precordial leads was documented in 2 patients, in apparent reversal of the pattern of progression observed in “classic” ARVC. Third, the septum is generally spared even in late-stage ARVC with LV involvement. In contrast, >50% of the clinical LDAC cohort had septal LGE. Fourth, isolated global RV dysfunction precedes LV involvement in the classic pattern of disease expression (10). In the LDAC cohort, however, >30% had LV dilation and/or impairment in the presence of preserved right-sided volumes and function.

“Classic” ARVC is characterized by RV preponderance throughout the disease course; the RV/LV volume ratio shows positive correlation with age and is typically ≥1.4 among individuals with advanced disease and LV involvement. The “biventricular” pattern is defined by parallel involvement of both ventricles, with the volume ratio remaining approximately 1 throughout the disease course. True LDAC is purported to mirror the “classic” pattern, with the LV consistently more severely affected than the RV. The RV/LV volume ratio is typically <1 in LDAC and is expected to correlate inversely with age. In both our earlier series and the present cohort, this inverse correlation was weak and failed to reach statistical significance (10). The reasons for this are 2-fold. First, the protocol of the current study employed arrhythmia of LV origin and (infero)lateral T-wave inversion as primary inclusion criteria: both key features of LDAC but also recognized in the “biventricular” subtype of arrhythmogenic cardiomyopathy. The corollary is a cohort that highlights the profile of nonclassic arrhythmogenic cardiomyopathy and its common misattribution to other disorders but might not wholly represent pure LDAC. Second, extensive LV LGE might precede the onset of global LV systolic dilation, limiting the utility of the RV/LV volume ratio as an indicator of early left-dominant disease and precluding its use in ascertainment of the cohort. In some cases, distinction between the left-dominant and biventricular patterns might not be possible until ventricular dilation ensues with disease progression.

**LDAC versus DCM.** Differentiating the LDAC phenotype from DCM is clinically important to guide risk stratification and familial evaluation. Regional disease involvement is suggestive of arrhythmogenic cardiomyopathy, particularly when RV abnormalities are prominent; aneurysms are almost pathognomonic. The pattern of LGE might be a further aid to diagnosis; mid-wall enhancement is observed in both LDAC and DCM, but subepicardial distribution raises suspicion of arrhythmogenic cardiomyopathy.

One of the defining characteristics of arrhythmogenic cardiomyopathy, and the principal means of distinction from DCM, is a predisposition to ventricular arrhythmia that exceeds the degree of morphological abnormality and systolic impairment. While frequent and complex ventricular arrhythmia is a recognized feature of DCM, and SCD...
accounts for at least 30% of the overall mortality, both occur in the context of overt systolic dysfunction. Furthermore, although a significant proportion of individuals with DCM compensate at New York Heart Association functional class I or II, heart failure is the primary mode of presentation. In contrast, among LDAC patients with clinically significant I or II, heart failure is the primary mode of presentation. Further mechanistic insight into the broad spectrum of arrhythmogenic cardiomyopathy awaits fresh gene identification and expression studies with phenotypic correlation.

Study limitations. Key limitations include referral bias due to recruitment of study patients from a tertiary center Inherited Cardiovascular Disease service. Furthermore, the case–mix was skewed by a paucity of index cases requiring evaluation for arrhythmia and a preponderance of relatives undergoing familial evaluation, reflecting the special interests of our center. Although its capacity to mimic other diseases might contribute to under–recognition, the true prevalence of LDAC remains unclear, pending systematic evaluation of patients with unexplained arrhythmia and ECG changes of LV origin in large, community-based populations.

Conclusions

We are able to summarize the salient clinical features of LDAC (Table 6) for incorporation into forthcoming revisions of the Task Force criteria, to facilitate diagnosis of left-dominant and biventricular disease variants. It should be emphasized that the unified conception of LDAC/IMF presented here is based predominantly on similarities in clinical profile. As in HCM and DCM, there is considerable phenotypic heterogeneity, incorporating fibrofatty and pure fibrotic forms. Both may occur in conjunction with desmosomal mutations, strengthening the premise that desmosomal dysfunction is the final common pathway. Nevertheless, molecular classification on this basis might be premature. The success rate from screening the known desmosomal genes in the LDAC cohort was approximately 30%, similar to that in unselected ARVC populations (22). Accepting that a significant proportion of the remainder might have mutations in other components of the desmosome, this is still unlikely to wholly account for the discrepancy, and extra-desmosomal genes will likely have to be sought. Transmembrane protein 43 has recently been implicated in ARVD5, which is associated with early and prominent LV involvement (36). The transmembrane protein 43 gene contains a response element for peroxisome proliferator–activated receptor–gamma, an adipogenic transcription factor that is also involved in epithelial cell differentiation; at this juncture, however, an association with desmosomal development and function remains speculative. Further mechanistic insight into the broad spectrum of arrhythmogenic cardiomyopathy awaits fresh gene identification and expression studies with phenotypic correlation.

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