Journal of the American College of Cardiology Vol. 52, No. 23, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.09.019

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).

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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

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Manuscript received July 23, 2008, accepted September 4, 2008.

JACC Vol. 52, No. 25, 2008
December 16/23, 2008:2175–87

Abbreviations and Acronyms

ARVC = arrhythmogenic right ventricular cardiomyopathy
CI = confidence interval
CMR = cardiovascular magnetic resonance
DCM = dilated cardiomyopathy
ECG = electrocardiogram
HCM = hypertrophic cardiomyopathy
IMF = idiopathic myocardial fibrosis
LBBB = left bundle branch block
LDAC = left-dominant arrhythmogenic cardiomyopathy
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVNC = left ventricular noncompaction
PVC = premature ventricular complex
RBBB = right bundle branch block
RV = right ventricle/ventricular
SCD = sudden cardiac death
VT = ventricular tachycardia
WMA = wall motion abnormality

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 infective 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, under-recognition 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 re-assessment 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 dilation/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 dilation/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

Table 1 Study Protocol

Stage 1
Inclusion criteria
One or more of the following:
• Ventricular arrhythmia of RBBB morphology
• Isolated (infero)lateral T-wave inversion
• Proven LDAC/IMF in the family
Exclusion criteria
Any of the following:
• Systemic arterial hypertension (>160/100 mm Hg documented and confirmed at repeated measurements and/or evidence of target-organ disease)
• Coronary artery disease (obstruction >50% of the luminal diameter in a major branch)
• Hypertrophic cardiomyopathy
• Previous or current clinical heart failure
• Inducible ischemia on stress test
• History of chronic excess of alcohol consumption
• Sustained, rapid, uncontrolled supraventricular arrhythmia
• Systemic diseases
• Pericardial diseases
• Congenital heart disease
• Cor pulmonale
Stage 2: inclusion criteria
For subjects entered on the basis of ventricular arrhythmia of RBBB morphology or isolated (infero)lateral T-wave inversion:
• Evidence of structural LV disease (dilation, systolic impairment, unequivocal WMA, or LGE)
For subjects entered on the basis of a family history of LDAC/IMF:
• Ventricular arrhythmia of RBBB morphology, isolated (infero)lateral T-wave inversion, or evidence of structural left-dominant disease (LV dilation/systolic impairment exceeding that of the RV; extensive LGE with preserved RV function)
Clinical evaluation
12-lead ECG
Signal-averaged ECG with a 40-Hz filter
2D echocardiography
Ambulatory ECG monitoring
Exercise testing ± metabolic gas exchange measurements (15)
CMR with protocol and consensus >2-reader review (D.J.P., W.J.M., S.S.C., S.K.P.) as previously described (14)
Mutation screening of 5 desmosomal genes (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2) by direct sequencing
(Endomyocardial biopsy taken from right side of interventricular septum at setting of device implantation)
Arrhythmia grading scale
0 Nil of significance or supraventricular arrhythmia only
1 <4 PVCs on exercise testing or <200 PVCs on 24-h Holter monitoring but including couplets and/or bigeminy
2 >200 PVCs/24 h on Holter or ≥4 PVCs on exercise testing or rare isolated NSVT with rate <200 beats/min and/or <6 consecutive beats
3 >400 PVCs/24 h on Holter or isolated NSVT on 2 or more tapes within 6 months or frequent ectopy and NSVT on exercise testing
4 >1000 PVCs/24 h on Holter or NSVT in the context of frequent PVCs
5 Recurrent NSVT with rate >200 beats/min and/or >6 consecutive beats accompanied by frequent PVCs
6 Sustained VT
CMR analysis
CMR-derived EDVs expressed as a percentage of predicted throughout to adjust for normal variations related to age, gender, and BSA (14,17,18)
Extent of LGE in the LV (LV lesion) was visually graded on a 5-point ordinal scale:
0 = nil;
1 = mild, affecting ≤2 segments;
2 = mild to moderate, affecting 3 segments;
3 = moderate to severe, affecting 4 segments;
4 = severe, affecting 5 or more segments

See references 14–18.

2D = 2-dimensional; BSA = body surface area; CMR = cardiovascular magnetic resonance; ECG = electrocardiogram; EDV = end-diastolic volume; IMF = idiopathic myocardial fibrosis; LDAC = left-dominant arrhythmogenic cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricular; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex; RBBB = right bundle branch block; RV = right ventricular; VT = ventricular tachycardia; WMA = wall motion abnormality.

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

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Table 2 Demographic and Clinical Profile of LDAC Cohort

Age, yrs (range)	44 ± 16 (14–81)
Gender, men/women	22/20
Asymptomatic	12 (29%)
Symptomatic	30 (71%)
Atypical chest pain	11 (26%)
Sustained palpitation	21 (50%)
Exertional dyspnea	2 (5%)
Pre-syncope	16 (38%)
Syncope*	5 (12%)
Family history	
Pathologically proven arrhythmogenic cardiomyopathy	27 (64%)
Pathologically proven IMF	5 (12%)
Clinical diagnosis of arrhythmogenic cardiomyopathy in relative	27 (64%)
SCD of unknown cause	18 (43%)
Proven familial disease	35 (83%; 95% CI 68%–92%)
12-lead ECG abnormalities	
T-wave inversion/flattening in V_5–V_6 ± V_4, I, aVL	16 (40%)
T-wave inversion/flattening in II, III, aVF	11 (27.5%)
T-wave inversion/flattening in V_1–V_6	3 (7.5%)
Left axis deviation (QRS axis $<-30°$)	5 (12.5%)
Leftward QRS axis ($-30° <$ QRS axis <0)	3 (7.5%)
Early transition	2 (5%)
Left bundle branch block	1 (2%)
Late potentials on SAECG (40-Hz filter)	17/33 (51%)
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)
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 (% predicted)	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%)
Documented ventricular arrhythmia (of LV or biventricular origin)‡	
Grade	
0	8 (19%)
1	0
2	6 (14%)
3	6 (14%)
4	16 (38%)
5	5 (12%)
6	1 (2%)
Tissue characterization by CMR†§	
Late enhancement in LV	40/40 (100%; 95% CI 89%–100%)
Pattern	
Subepicardial	12 (30%)
Mid-wall	5 (12.5%)
Both	23 (57.5%)
Extent	
Grade I (mild)	8 (20%)
Grade II (mild to moderate)	6 (15%)
Grade III (moderate to severe)	7 (17.5%)
Grade IV (severe)	19 (47.5%)
Location	
Septum	22 (55%; 95% CI 39%–70%)
Inferior wall	32 (80%)
Inferolateral wall	37 (92.5%)
Anterolateral wall	20 (50%)
Anterior wall	8 (20%)

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, 15 (45%) 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; SAECG = signal-averaged electrocardiogram; SCD = sudden cardiac death; other abbreviations as in Table 1.

acute chest pain, associated in 2 with troponin rise. The remainder achieved a good workload on exercise testing without chest pain or ST-segment changes (Duke treadmill score >5). None reported orthopnea, paroxysmal nocturnal dyspnea, or ankle swelling; physical signs of heart failure were absent.

Serial electrocardiograms (ECGs) obtained over 5 years were available in 3 individuals. Two had T-wave flattening/inversion in V_5 to V_6 on initial evaluation. This gradually extended to V_4, V_3, V_2, and the inferior leads during follow-up. In 1 of these patients, the evolution of repolarization abnormalities in the right precordial leads coincided with the appearance of prominent aneurysmal changes in the free wall of the RV on annual cardiovascular magnetic resonance (CMR) examinations. A third patient showed gradual anti-clockwise rotation from a normal QRS axis to left axis deviation.

Structural abnormalities. Imaging results are summarized in Table 2. By CMR, 7 patients had left ventricular end-diastolic volume (LVEDV) exceeding 150% of pre-

Table 3 Summary of Desmosomal Gene Changes Isolated in LDAC Cohort

Gene	Nucleotide Change	Predicted Effect	n	Comment
DSP	3337C→T	Nonsense; premature termination (R1113X)	1	Family A
DSP	3045delG	Frameshift; premature termination (S1015fsX1017)	4	Family B
DSP	1325C→T	Missense (S442F)	1	Family C In highly conserved amino acid region (N-terminal)
DSP	1520C→T	Missense (S507F)	2	Family D In highly conserved amino acid region (N-terminal)
DSP	1755insA	Frameshift; premature termination (T586fsX594)	4	Family E Previously published* (2034insA)
DSP	939+1G→A	Mutant splice product; premature termination	1	Family F Previously published*
PKP-2	419C→T	Missense (S140F)	1	Previously published*
DSG-2	1773_1774delTG	Frameshift; premature termination C591X	1	Extracellular anchor domain (previously published)*

*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

Table 4 Events Recorded in LDAC Cohort

63/M	Background of persistent atrial fibrillation, treated with digoxin and warfarin.
	Presented with out-of-hospital VF arrest. No evidence of digoxin toxicity.
	Resting 12-lead ECG: sinus rhythm with inferolateral T-wave inversion.
	Monitoring: sinus rhythm with nonsustained VT of RBBB morphology.
	Angiogram: unobstructed coronary arteries.
	CMR: mild LV dilation and systolic dysfunction (LVEF 42%), with basal and septal midwall LGE.
	ICD placement. Free from interventions at 11-month follow-up.
81/F	Presented locally with pre-syncope and sustained VT of RBBB morphology.
	Resting 12-lead ECG: sinus rhythm with LBBB.
	2D-echocardiogram: mild LV systolic dysfunction (LVEF 48%) with inferior WMA.
	Angiogram: unobstructed coronary arteries.
	Cardiac monitoring discontinued after oral loading with amiodarone and a 72-h arrhythmia-free interval, but subsequently found unresponsive in bed and asystolic.
	Post-mortem: heart weight 342 g; nondilated LV; thinning of circumferential LV; fine interstitial fibrosis in lateral and inferior walls.
51/M	Presentation age 46 yrs with sustained palpitation and pre-syncope; nonsustained VT of LV origin on exercise test and Holter. Echocardiogram: LVEDD 5.5 cm, LVESD 4.6 cm, and LVEF 40%. Angiographically normal coronary arteries. Presumed diagnosis of dilated cardiomyopathy; treated with angiotensin-converting enzyme inhibitor and beta-blocker. Improvement noted on follow-up echocardiogram (LVEDD 5.1 cm, LVEF 50%).
	CMR showed apical, lateral, and inferolateral WMA and extensive, patchy midwall LGE. In spite of revision of diagnosis to LDAC, no further measures were taken owing to prolonged symptomatic stability. Suffered SCD in his sleep 5 yrs after first presentation. Post-mortem: diffuse interstitial fibrosis encircling individual cardiac myocytes; focal chronic inflammation. Diagnosis: idiopathic myocardial fibrosis.

EDD = end-diastolic dimension; ESD = end-systolic dimension; other abbreviations as in Tables 1 and 2.

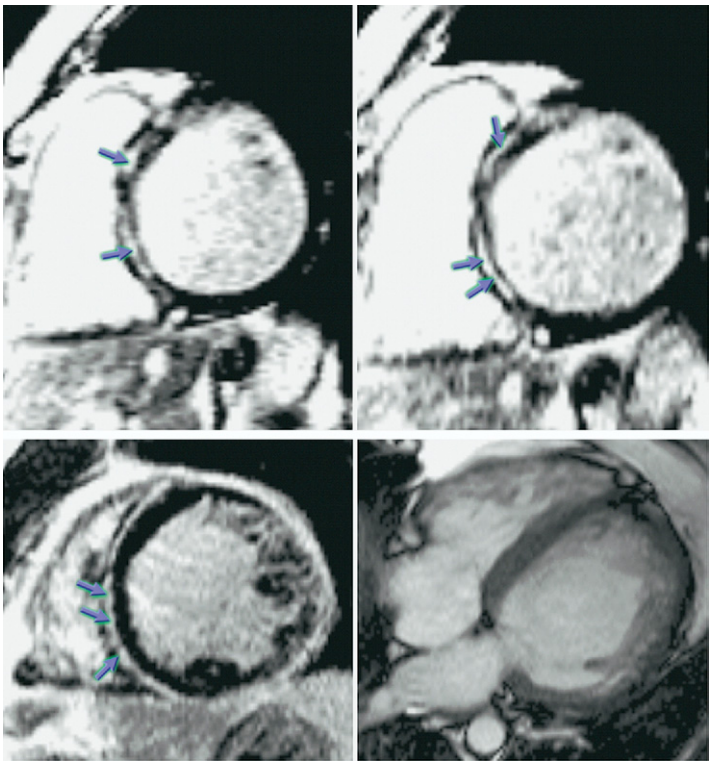

Figure 1 **Patterns of Late Enhancement in LDAC**

Magnetic resonance images from 2 patients in the left-dominant arrhythmogenic cardiomyopathy (LDAC) cohort, both of whom presented in the fifth decade of life with syncope and were found to have nonsustained ventricular tachycardia of left ventricular (LV) origin. Both had unobstructed coronary arteries. The first had late gadolinium enhancement (LGE) in a midwall distribution **(arrows)**, patchy in basal cuts **(upper left)** but becoming more confluent at mid-level **(upper right)**. The second had near-circumferential LGE **(lower left)** and marked LV dilation with preserved right ventricular volumes **(lower right)**, far exceeding the LV enlargement observed in the remainder of the cohort. Neither had symptoms of heart failure.

burden of premature ventricular complexes (PVCs) of RBBB morphology, and 1 also had T-wave inversion in V_4 to V_6, 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.

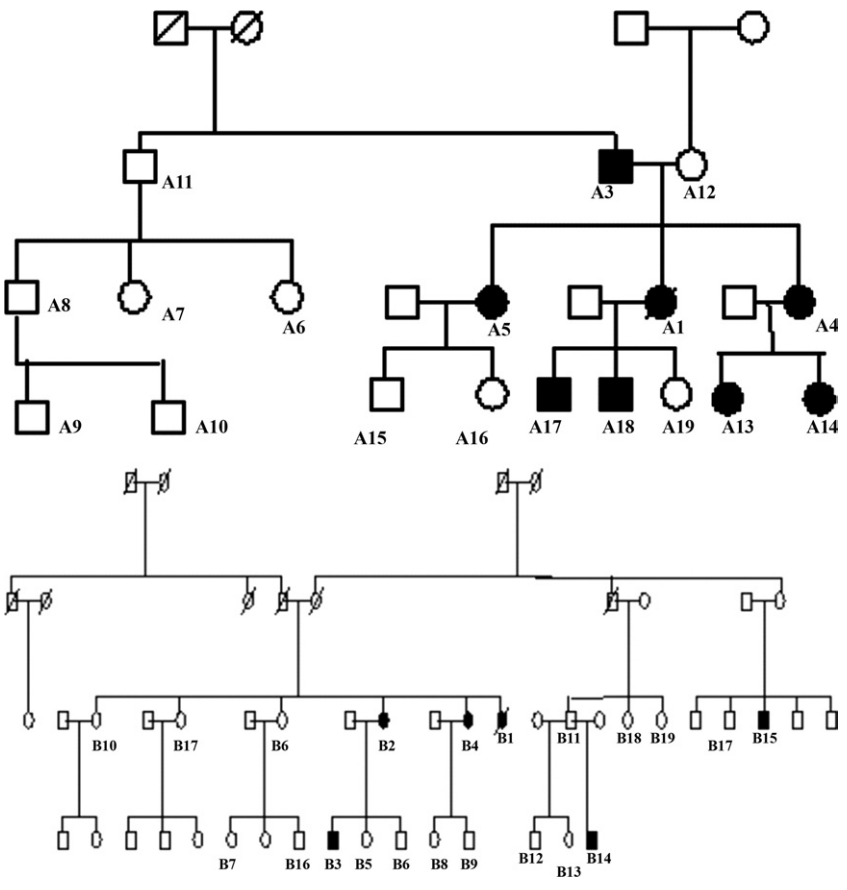

Figure 2 **Pedigrees From Families A and B**

Novel mutations in desmoplakin were identified in families A **(upper panel)** and B **(lower panel)**. Both mutations are predicted to result in premature termination of protein translation. Genetically affected male subjects **(squares)** and female subjects **(circles)** are shown as **solid black**.

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

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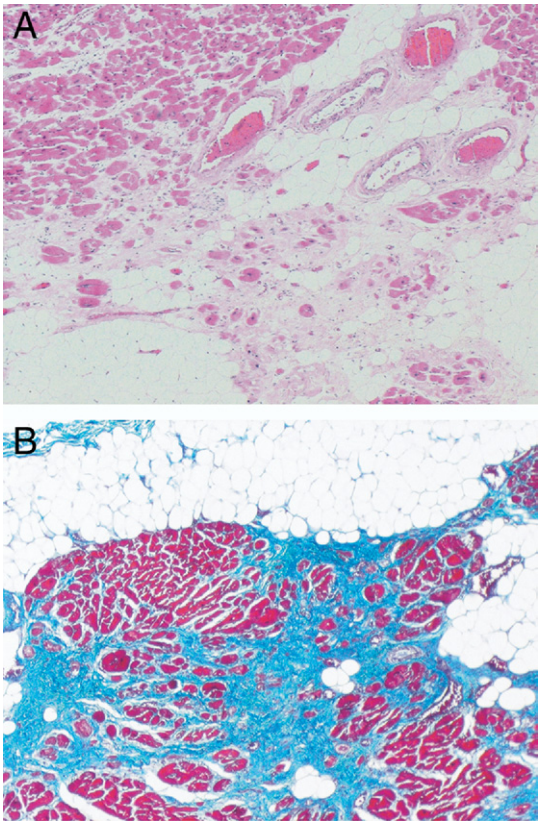

Figure 3 **Histology From Proband in Family A**

The proband (A1) died suddenly at age 35 years. Post-mortem examination revealed subepicardial fibrosis extending from the inferior left ventricular wall to the septum and lateral wall. Histology showed **(A)** myocytes surrounded by fibrous tissue and sarcoplasmic vacuolization with hematoxylin and eosin staining and **(B)** increase in fibrous tissue **(blue-green)** with modified Masson's trichrome staining.

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

	Age, yrs/Gender	
		Family A (Pedigree, Fig. 2) (3337C→T Mutation in DSP)
A1	35/F*	Proband suffered SCD aged 35 yrs after prodrome of palpitation and pre-syncope.
		Post-mortem examination: mildly depressed linear scar, approximately 2–3 mm in from the epicardium, running around the inferior wall of the LV to the septum and extending out to the lateral wall. Histology revealed fibrosis with some fat and a few islands of surviving myocytes (Fig. 3). The RV showed thinning and adipose replacement but no fibrosis.
A3†	72/M	Asymptomatic, age 64 yrs, at initial family screening. No late potentials; normal echocardiogram.
		Over next 8 years, developed late potentials on SAECG and LV dilation with mild systolic impairment (LVEDD 6.1 cm, LVEF 50%) on echocardiography. Frequent PVCs of biventricular origin were observed on exercise testing and Holter monitoring (500/24 h).
		Nine years after first evaluation, presented to local hospital with severe chest pain and diaphoresis. Troponin T raised at 0.69. Presumed diagnosis of non–ST-segment elevation MI, but coronary arteries unobstructed on angiography. During subsequent follow-up, found to have new ECG abnormalities, with T-wave inversion/flattening in V_5 to V_6 and inferiorly. CMR revealed aneurysms at the RVOT, subtricuspid region, and mid-free wall, and extensive subepicardial and midwall LGE in the LV, sparing only the anterior wall.
A4†	37/F	Palpitation and pre-syncope; T-wave inversion in V_1 to V_3 (dynamic and associated with symptomatic exacerbations); 1,000 ventricular extrasystoles/24 h; RV aneurysms and LGE in inferior and inferolateral LV walls on CMR.
A5†	42/F	Palpitation and pre-syncope; epsilon waves in V_1 to V_2; ventricular extrasystoles of LBBB and RBBB morphology on exercise testing; CMR showed RV aneurysms and extensive LGE affecting inferior and lateral LV walls.
A17	12/M	Asymptomatic. Moderate biventricular dilation on CMR.
A18	13/M	Asymptomatic. RV WMA on CMR.
		Family B (Pedigree, Fig. 2) (3045delG mutation in DSP)
B1	26/F*	Proband suffered SCD aged 26 yrs after prodrome of palpitation and syncope. No history of dyspnea; extremely fit and active. Collapse while playing squash; resuscitation efforts successful, but treatment withdrawn on critical care unit after she remained unresponsive off sedation and head CT scan confirmed severe hypoxic brain damage.
		Post-mortem examination: heart weight 330 g with severe LV and mild RV dilation. Myocardium appeared diffusely abnormal with pallor in most regions, and scattered punctate areas of congestion. Histology revealed areas of necrosis, with focal infiltrates of chronic inflammatory cells and patchy neutrophil accumulation around the necrotic myocytes. Final cause of death cited as acute cardiac failure due to viral myocarditis.
B2†	43/F	Presented locally with sustained palpitation and pre-syncope; symptoms longstanding but worsening. No signs or symptoms of heart failure. 12-lead ECG: early transition and T-wave inversion in V_3 to V_6. 2D-echocardiogram showed mildly dilated LV (LVEDD 5.5 cm) with moderate systolic impairment (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.
		Referred for genetic studies. Exercise testing: peak oxygen consumption 24.6 ml/kg/min (91% of predicted); multiple PVCs and nonsustained VT of both LV and RVOT origin observed. Arrhythmic symptoms improved substantially after introduction of amiodarone. CMR revealed RV aneurysms at subtricuspid region and mid-free wall and WMA at the outflow tract and apex. LV apex dilated and dyskinetic. Extensive LV LGE observed in circumferential pattern (Fig. 4).
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, lateral T-wave changes, and frequent, complex ventricular arrhythmia of biventricular origin, and preserved LV function on 2D-echocardiography, initially reassured that her symptoms were benign.
		Recruited for family assessment. Contrast echocardiography: heavily trabeculated LV apex that fulfilled criteria for LVNC. Nevertheless, RV WMA at triangle of dysplasia raised suspicion of ARVC. CMR reproduced these findings and additionally demonstrated circumferential LGE. Endomyocardial biopsy showed myocyte loss and fibroadipose replacement.
B11		Brief, infrequent episodes of palpitation. Left-axis deviation and lateral T-wave inversion on 12-lead ECG; frequent and complex arrhythmia of both RBBB and LBBB morphology on exercise testing and Holter monitoring; multiple WMA in both ventricles with extensive near-circumferential LV LGE (Fig. 4). Remains well on beta-blocker therapy.
		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.
		Cardiovascular evaluation: atypical chest pain and palpitation; unifocal ventricular extrasystoles and nonsustained VT with RBBB configuration and left-axis deviation. Electrophysiology opinion: morphology considered characteristic of left posterior fascicular VT, although patient declined formal electrophysiological studies. Beta-blockers for symptom relief were mainstay of therapy until contrast echocardiography and CMR revealed typical RV WMA and prominent LV LGE. Amiodarone subsequently commenced with near-complete resolution of symptoms.
		Family D (1520C→T mutation in DSP)
D1	32/M*	Suffered SCD after prodrome of 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 V_5, V_6, I, and aVL. Frequent PVCs of both LV and RVOT origin. CMR: LV mildly dilated; LVEF 43%; extensive circumferential 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; equivocal R-wave progression; flattened T waves in I, V_5 to V_6, 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 dilation and WMA at RVOT and subtricuspid region, with extensive LV LGE including septum.

*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.

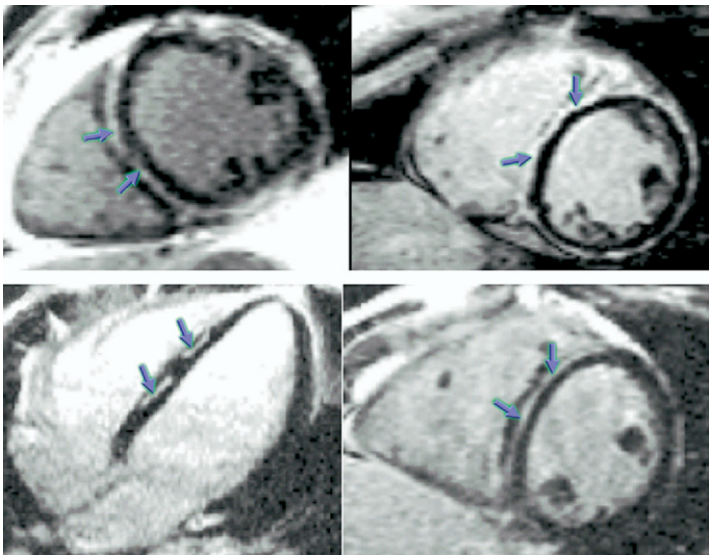

Figure 4 Magnetic Resonance Images From Family B

Late gadolinium enhancement (LGE) in 3 members of family B: B11 **(top left)**, B2 **(top right)**, and B3 **(lower panels)**. In B11 **(top left)**, the septum shows prominent midwall LGE **(arrows)**, which tracks around in a near-circumferential pattern. In B2 **(top right)**, subepicardial LGE **(arrows)** is seen as a circumferential band in the outer one-third of the myocardium and the right side of the interventricular septum. In B3 **(lower panels)**, 2 areas of midwall LGE **(arrows)** are discernible in the septum on the **left-hand** 4-chamber view, 1 of which is reproduced in the short-axis cut on the **right.** B3 was distinguished by an otherwise normal cardiovascular evaluation. All affected relatives had the 3045delG mutation in desmoplakin.

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 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

Table 6 Clinical Diagnostic Features of LDAC*

ECG	Unexplained T-wave inversion in V_5, $V_6 \pm V_4$, I, and aVL
Arrhythmia	Sustained or nonsustained ventricular tachycardia of RBBB configuration documented on ECG or Holter monitoring or during exercise testing
	Frequent ventricular extrasystoles (RBBB morphology)
Imaging	LV aneurysms
	Mild LV dilation and/or systolic impairment (with arrhythmic presentation)*
Biopsy/CMR	Myocyte loss with fibrofatty replacement on histology
	Extensive LGE of LV myocardium (with subepicardial/midmyocardial distribution)

*The distinction from dilated cardiomyopathy is made on clinical grounds, as discussed earlier.
Abbreviations as in Table 1.

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 ventricular arrhythmia (grade ≥2), the mean LVEF on CMR was 54 ± 11%. Events in the LDAC population, including both the clinical cohort and deceased index cases, occurred in apparently fit individuals; premonitory symptoms, if any, were palpitation and syncope. None had signs or symptoms of clinical heart failure, although a proportion of patients with arrhythmogenic cardiomyopathy may develop this complication late in the disease course. Arrhythmic control and prevention of SCD are therefore the foremost goals of therapy in LDAC; relatively preserved LV systolic function may belie significant risk of events.

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.

Acknowledgments

The authors are indebted to Ricardo Wage, DCR(R), and Gillian C. Smith, MSc, for CMR technical support, and to Sripurna Das, PhD, for her helpful comments on the manuscript. This work is dedicated to the memory of Michael J. Davies, MD, FRCP, FRCPath, who recognized the LDAC/IMF phenotype and predicted its association with ARVC over a decade ago.

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Key Words: arrhythmia ■ cardiomyopathy ■ electrocardiography ■ genetics ■ magnetic resonance imaging ■ sudden death.