JACC Vol. 31, No. 1
January 1998;195–201

Familial Dilated Cardiomyopathy: Cardiac Abnormalities Are Common in Asymptomatic Relatives and May Represent Early Disease

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Objectives. **This study sought to determine whether early disease is identifiable in asymptomatic relatives of patients with dilated cardiomyopathy (DCM) by means of noninvasive cardiologic assessment.**

Background. **DCM is diagnosed on the basis of advanced heart failure, where cardiac dilation and impaired contractility are recognized in the absence of a recognized etiology (World Health Organization criteria). However, initial clinical presentation may be with severe complications: thromboembolism, arrhythmia or sudden death. DCM has recently been recognized to be familial, with autosomal dominant inheritance in many cases. Familial disease is present in 9% to 20% of patients with DCM, and the ability to identify early disease in such people may improve patient management and aid in the understanding of pathogenesis.**

Method. **We prospectively assessed 408 asymptomatic relatives (mean [±SD] age 35 ± 15 years, 193 men) of 110 consecutive patients with DCM by means of history and physical examination, two-dimensional echocardiography, 12-lead and signal-averaged electrocardiography and metabolic exercise testing. We hypothesized that signs of lesser cardiac dysfunction in such relatives might indicate early disease.**

Results. **Twenty-nine percent of relatives had abnormal results on the echocardiogram. Twenty percent (n = 45) had left ventricular enlargement (LVE), defined as LV end-diastolic diameter (LVEDD) ≥112% predicted; 6% (n = 13) had depressed fractional shortening (dFS), defined as FS ≤25%; and 3% (n = 7) had frank DCM, defined as LV dilation, impaired contractile performance and LVEDD ≥112% plus FS ≤25%. Other abnormalities of cardiac function were identified in relatives with LVE or dFS: A greater number with LVE had an abnormal metabolic exercise test result than normal relatives (9% vs. 1%, p < 0.05). Relatives with LVE and abnormal maximal oxygen consumption (Vo_2max) (defined as Vo_2max <80% predicted) had a lower absolute Vo_2max than normal relatives (30 ± 8 vs. 43 ± 9 ml/min per kg, p = 0.01). The QRS duration (at the 25-Hz filter) on the signal-averaged electrocardiogram was prolonged in relatives with LVE (103 ± 13 ms) and dFS (102 ± 12 ms) compared with that of normal relatives (97 ± 12 ms, p < 0.05). Over a mean 39-month follow-up period, 12 relatives with LVE (27%) and none with dFS developed symptomatic DCM (p < 0.0001). One relative with LVE died suddenly, and another underwent heart transplantation.**

Conclusions. **Nearly one-third of asymptomatic relatives (29%) have echocardiographic abnormalities, and 27% of such relatives progress to development of overt DCM. Early identification of such people would permit appropriate intervention that might influence the serious complications and mortality of this disease.**

(J Am Coll Cardiol 1998;31:195–201)

Dilated cardiomyopathy (DCM) is diagnosed on the basis of clinical features of advanced heart failure, with severe left ventricular (LV) dilation and impaired contractile performance, after exclusion of other known etiologic factors, according to the criteria defined by the World Health Organization (1). Patients may present with thromboembolism, arrhythmia or sudden death before heart failure is manifest. Disease is therefore advanced on presentation when other noninvasive investigations are also abnormal: Signal-averaged electrocardiographic (ECG) abnormalities have been shown to indicate underlying myocardial fibrosis (2), and metabolic exercise testing demonstrates a reduction in cardiac function (3,4).

In a proportion of cases, DCM is now recognized as a familial condition (5,6), with Mendelian autosomal dominant inheritance; thus, first-degree relatives have a higher risk of developing the disease. Such people may be identifiable by a lesser degree of cardiac dilation and contractile impairment than are conventionally accepted for a diagnosis of DCM.

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Manuscript received October 18, 1996; revised manuscript received August 21, 1997, accepted September 29, 1997.

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Published by Elsevier Science Inc.

0735-1097/98/$19.00
PII S0735-1097(97)00433-6

Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
DCM	=	dilated cardiomyopathy
dFS	=	depressed fractional shortening
ECG	=	electrocardiogram, electrocardiographic
FS	=	fractional shortening
LVE	=	left ventricular enlargement
LVEDD	=	left ventricular end-diastolic diameter
LVEDD%	=	left ventricular end-diastolic diameter expressed as percent of left ventricular end-diastolic diameter predicted from body surface area
RMS	=	root mean square
Vo_2max	=	peak oxygen uptake achieved on symptom-limited treadmill exercise testing

Currently, there are no criteria for the definition or recognition of early disease in DCM. The ability to identify asymptomatic people with early disease is a goal in the prevention of complications and understanding of disease pathogenesis.

We speculated that relatives of affected patients may display clinical markers of early disease, before any symptoms are manifest. Our aim was to prospectively characterize relatives of patients with DCM, by means of noninvasive clinical cardiologic evaluation, to assess whether abnormalities were recognizable and to determine the frequency of progression of such abnormalities to DCM over time.

Methods

Patient characterization. Between November 1992 and February 1996, 110 consecutive patients with idiopathic DCM, as defined by World Health Organization criteria (1) (LV diastolic diameter >2.7 cm/m^2 and LV ejection fraction <40% or fractional shortening <25%, with active exclusion of ≥50% obstruction of one or more coronary arteries, active myocarditis or any specific primary or secondary heart muscle disease assessed by echocardiography, angiography and right ventricular biopsy) were evaluated.

An extended family pedigree was constructed for each patient, from which each relative was contacted and offered appropriate counseling and screening for DCM. Of a total of 430 relatives contacted, 408 (mean [±SD] age 35 ± 15 years, 193 male) from 89 families agreed to be screened (95% screening rate). Of these 408, 54 (13%) were excluded from further analysis because they were <16 years old; and 79 (19%) were excluded because of known, long-standing hypertension (blood pressure >150/90 mm Hg for >1 year) or long-term high alcohol intake (men: >21 U/week; women: >14 U/week [1 U = 1 glass of table wine, ½ pint of beer, 1 measure of spirits or 1 measure of sherry]). A further 50 relatives with insufficient data (12%), primarily because of geographic limitations such as residence outside the United Kingdom and an inability to travel, were also excluded from analysis, leaving 225 relatives (35 ± 15 years old, 109 men) available for analysis.

Each relative underwent assessment by medical history, full clinical examination, 12-lead ECG, signal-averaged ECG, two-dimensional echocardiogram and maximal symptom-limited treadmill exercise testing with respiratory gas sampling.

Echocardiographic studies. All echocardiograms were acquired by the same experienced operator who had no knowledge of the patients' clinical data by means of high quality echocardiographic equipment (Hewlett-Packard 77020A or Acuson 128XP/10c). Two-dimensional and M-mode echocardiography were performed using conventional techniques. Measurements were taken from an M-mode long-axis left parasternal view of LV wall thickness, ventricular cavity dimension in systole and diastole at the level of the mitral valve tips and E and A wave filling velocities through the mitral valve. From these measurements, the percent fractional shortening (FS) and E/A ratio were calculated according to standard techniques. All studies were reviewed for accuracy by a second independent interpreter. Echocardiographic studies were repeated in 20 relatives (44%) with LV enlargement (LVE) and 16 normal relatives (10%) within 6 months of the initial scan to provide an internal quality control for the echocardiograms.

Using the formula of Henry et al. (7), the predicted LV end-diastolic diameter (LVEDDc) was calculated from each patient's height and weight and thus body surface area (BSA):

$$\text{LVEDDc (predicted)} = 45.3 \times \text{BSA}^{0.3} - 0.03 \times \text{Age} - 7.2.$$

The measured LVEDD was then expressed as a percent according to the ratio

$$\text{LVEDD\%} = \text{LVEDD/LVEDDc}.$$

LVEDD% ≥112% was chosen as the upper limit for normality because this value represents 2 SD above the mean value in Henry's own data and was also previously confirmed by our own review of 239 echocardiograms in normal subjects (data not shown).

Two types of cardiac abnormalities were defined among asymptomatic relatives: 1) LVE, where the left ventricle was enlarged compared with that predicted according to the formula of Henry et al. (7) (LVEDD% ≥112%) but with functional capacity, as determined by percent fractional shortening, was maintained; and 2) isolated depressed fractional shortening (dFS), where ventricular contractility was reduced (FS <25%), but ventricular cavity dimensions were within the predicted range. The clinical characteristics of patients in each of these groups are shown in Table 1.

Metabolic exercise testing. Maximal symptom-limited metabolic exercise testing was performed using the standard Bruce protocol with a Marquette MAX-1 treadmill and a dedicated cart and respiratory gas sampling through a tight-fitting face mask and an MGA 110 medical gas analyzer (Marquette Anesthesia and Respiratory Care Corporation), Ventilation Measurement Module VMM2 (Interface Associates), with software by Breath by Breath Respiratory Data Collection Systems (First Breath Inc.), according to established techniques (8). Oxygen consumption was determined using a

Table 1. Characteristics of Individual Groups of Relatives

	DCM (n = 7)	LVE (n = 45)	dFS (n = 13)	Normal (n = 160)	LVE Progressing to DCM (n = 12)
Age (yr)	34.4 ± 17.2	36.0 ± 14.9	37.2 ± 16.6	35.0 ± 14.7	40.7 ± 22.4
M/F	5/2	27/18	9/4	70/90	7/5
Race					
White	7	44	13	151	11
Black	0	0	0	4	0
Asian	0	1	0	5	1

Data presented are mean value ± SD or number of relatives. DCM = dilated cardiomyopathy; dFS = depressed fractional shortening; F = female; LVE = left ventricular enlargement; M = male.

temperature-controlled polargraphic sensor. Age-predicted maximal oxygen consumption (Vo_2max) was calculated using standard formulas (9).

Signal-averaged ECG. Signal averaged ECGs were recorded from the orthogonal leads of an Arrhythmia Research Technologies model 30050 machine, with standard software. Two hundred fifty beats were averaged and stored for later analysis, when all measurements and computations were made automatically without manual intervention.

Time domain analysis was performed at high pass filter settings of 25 and 40 Hz using a bidirectional four-pole Butterworth filter. After amplification, averaging and filtering, the signals were combined into a single vector magnitude $(x^2 + y^2 + z^2)^{1/2}$, and three conventional time domain indexes were calculated: duration of the total QRS complex; duration of the low amplitude (<40 μV) signals of the terminal portion of the QRS complex; and the root mean square (RMS) voltage of the terminal 40 ms of the QRS complex. Results were considered abnormal when at least two of the three conventional variables were beyond the normal range (total QRS duration >120 ms; low amplitude [<40 μV] signals >40 ms; and RMS voltage in the terminal 40 ms of the QRS complex <25 μV at the 25-Hz filter setting).

Statistical analysis. Chi-square analysis, Fisher exact test, unpaired two-tailed Student *t* test or stepwise logistic regression analysis was used as appropriate. Tests were performed using C-Stat (Cherwell Scientific, Oxford, UK) or SPSS (SPSS Inc.) software, on an IBM PC. A value <0.05 was considered statistically significant. Results are expressed as mean value ± SD.

Results

Echocardiographic studies. Of 225 relatives assessed, 7 (3%) were found to have DCM, 45 (20%) LVE and 13 (6%) dFS; 160 (71%) were echocardiographically normal.

Relatives determined to have LVE had, in addition, significantly impaired LV function compared with normal relatives (FS: 33 ± 5% vs. 36 ± 6%, p = 0.01). Relatives determined to have dFS only had, in addition, significant LVE compared with normal relatives (LVEDD%: 112 ± 13% vs. 102 ± 7%, p < 0.001).

Table 2. Clinical Characteristics of Relatives With Left Ventricular Enlargement

	Relatives With LVE (n = 45)	Normal Relatives (n = 160)	p Value
Age (yr)	35 ± 16	32 ± 15	0.27
LA diameter (mm)	35 ± 5	33 ± 5	0.001*
%FS	33 ± 5	36 ± 6	0.01*
Total exercise time (min)	12.8 ± 3.1	12.4 ± 2.7	0.53
QRS 25 (ms)	103 ± 13	97 ± 12	0.02*
LPD 25 (ms)	29 ± 11	25 ± 8	0.05*
RMS 25 (mV)	57 ± 37	77 ± 51	0.06
QRS 40 (ms)	98.1 ± 11.4	95.3 ± 10.6	0.22
LPD 40 (ms)	30.4 ± 10.5	26.6 ± 9.5	0.06
RMS 40 (mV)	41.7 ± 23.5	53.1 ± 35.8	0.1
Absolute Vo_2max (ml/min per kg)	40 ± 9.9	37 ± 8.8	0.38
LVEDD (mm)			
Abnormal Vo_2max	56.5 ± 3.4	46 ± 3.6	0.005*
Abnormal SAECG	56.7 ± 3.6	45.5 ± 6.4	0.004*
Initial echo study	55.4 ± 4	48 ± 4	
Repeat echo study	54.9 ± 4†	50.6 ± 5‡	

*Significant difference. †p = 0.73, ‡p = 0.1, initial versus follow-up left ventricular end-diastolic diameter (LVEDD). Data presented are mean value ± SD. echo = echocardiographic; LA = left atrial; LPD 25 = low amplitude signal duration at 25-Hz filter setting; LPD 40 = low amplitude signal duration at 40-Hz filter setting; LVE = left ventricular enlargement; QRS 25 = QRS duration at 25-Hz filter setting; QRS 40 = QRS duration at 40-Hz filter setting; RMS 25 = root mean square voltage at 25-Hz filter setting; RMS 40 = root mean square voltage at 40-Hz filter setting; SAECG = signal averaged electrocardiogram; Vo_2max = maximal oxygen consumption; %FS = percent fractional shortening.

Relatives with both LVE and dFS had significantly enlarged left atria compared with normal relatives (LVE: 35 ± 5 vs. 33 ± 5 mm, p = 0.001; dFS: 39 ± 4 vs. 33 ± 5 mm, p = 0.04). The measured E/A ratio in all relatives was significantly lower than predicted values (1.55 ± 0.83 vs. 1.75 ± 0.44, p = 0.03). In subjects with LVE, the E/A ratio was significantly lower than in normal relatives (1.29 ± 0.72 vs. 1.60 ± 0.71, p = 0.04).

There was no significant change in LVEDD in subjects who underwent repeat echocardiography within 6 months of the initial scan for either the LVE or normal group (Table 2). This finding indicates that an initial echocardiographic diagnosis of LVE or normality could be confidently repeated within 6 months, suggesting that LVE in these circumstances is not an ephemeral finding.

Clinical findings. Results of clinical examination of the cardiovascular system were abnormal in a greater proportion of subjects with LVE and dFS than in relatives with normal LV function. The majority of abnormal findings were minor, and no relative had signs of overt heart failure; there were signs of either a third or fourth heart sound, and two subjects had elevation of jugular venous pressure. One patient had a pansystolic murmur.

Thirty-one percent (n = 4) of subjects with dFS had abnormal examination results compared with only 4.7% (n =

Table 3. Clinical Characteristics of Relatives With Depressed Fractional Shortening

	Relatives With dFS (n = 13)	Normal Relatives (n = 160)	p Value
Age (yr)	35.4 ± 17.2	32.0 ± 15	0.43
LA diameter	39 ± 4	33 ± 5	0.04*
LVEDD (mm)	50.2 ± 4	48 ± 4	0.09
LVEDD%	112 ± 13	102 ± 7	<0.001*
Total exercise time (min)	13.9 ± 1.9	12.4 ± 2.7	0.38
QRS 25 (ms)	104 ± 11	99 ± 12	0.28
LPD 25 (ms)	24 ± 8	25 ± 12	0.85
RMS 25 (mV)	53.8 ± 19	77 ± 51	0.21
QRS 40 (ms)	101.6 ± 11.7	94 ± 10.4	0.05*
LPD 40 (ms)	30.5 ± 6.8	26.1 ± 9	0.26
RMS 40 (mV)	30 ± 8.9	57.6 ± 39.6	0.05*
Absolute Vo_2max (ml/min per kg)	42.9 ± 7.7	38.1 ± 8.9	0.31

*Significant difference. Data presented are mean value ± SD. Abbreviations as in Tables 1 and 2.

8) of normal relatives ($p < 0.0001$). In relatives with LVE, 10.4% (n = 5) had abnormal examination results ($p < 0.01$ vs. normal relatives).

Exercise testing and signal-averaged electrocardiography. There were significant metabolic exercise test abnormalities in relatives with LVE. A greater number of relatives with LVE had abnormal Vo_2max values compared with normal relatives (4.9% vs. 2.1%, $p < 0.05$). In relatives with LVE and abnormal Vo_2% (<80% predicted), there were significantly lower absolute Vo_2max values than in normal relatives (30 ± 7.8 vs. 42.5 ± 9.1 ml/min per kg, $p = 0.01$). LVEDD was smaller in subjects with LVE and abnormal Vo_2max values, than in those with normal Vo_2max values (45.6 ± 1.9 vs. 49.4 ± 2.3 mm, $p = 0.01$), suggesting that the observed metabolic impairments in LVE are not simply a function of a dilated ventricle.

In subjects with LVE, there were other abnormalities on signal-averaged electrocardiography: QRS duration (at 25 Hz): 103 ± 13 versus 97 ± 12 ms, $p = 0.02$; low amplitude signal duration (at 25 Hz): 29 ± 11 versus 25 ± 8 ms, $p = 0.05$ (Table 2). Relatives with dFS had a lower RMS voltage (at 40 Hz) (30 ± 8.9 vs. 57.6 ± 39.6 mV, $p = 0.05$) and a longer total QRS duration (at 40 Hz) (101.6 ± 11.7 vs. 94 ± 10.4 ms, $p = 0.05$) than normal subjects (Table 3).

Table 4. Progression of Disease During Follow-Up Period of 39 ± 14 Months

Initial Assessment		Follow-Up Assessment		
Group	No. (%)	Progression to	No. (M/F)	Age (yr)
DCM	7 (3%)	N/A		
LVE	45 (20%)	DCM	12 (7/5)	40.7 ± 22.4
dFS	13 (6%)	LVE or DCM	0	
Normal	160 (71%)	LVE	3 (1/2)	22.7 ± 5.9

Data presented are mean value ± SD or number (%) of relatives. Abbreviations as in Tables 1 to 3.

Table 5. Logistic Regression: Relation Between Progression of Left Ventricular Enlargement to Dilated Cardiomyopathy and Main Noninvasive Variables

Variable	Beta-Coefficient	Probability
%FS	−0.05	0.14
LVEDD	0.12	0.01
Vo_2max	0.001	0.96
LPD 25	−0.21	0.21
QRS 25	0.19	0.46
RMS 25	0.003	0.92
LPD 40	0.03	0.74
QRS 40	−0.15	0.60
RMS 40	−0.01	0.90

Abbreviations as in Table 1.

Follow-up data. Over a prospective follow-up period of 39 ± 14 months (median 39, range 14 to 59), 12 relatives with LVE (27%) and none with dFS developed DCM ($p < 0.0001$). No relatives who were assessed initially as normal developed DCM, but three (2%) progressed to develop LVE (Table 4).

One relative who progressed from LVE to DCM underwent successful heart transplantation. Two relatives with LVE died (sudden cardiac death in one with mild palpitations, and noncardiac death in one).

Stepwise logistic regression analysis using SPSS 6.0 software found a predictive association between LVEDD and the likelihood of progression to DCM from LVE, but no other single metabolic or ECG variable had predictive value (Table 5).

Familial clustering. The present study elucidated familial clustering of people with DCM, LVE and dFS; the prevalence of familial disease when LVE was included in the analysis was 48% (110 probands, 45 with LVE, 7 with DCM). Two main patterns of inheritance were seen: The majority of pedigrees studied appear to conform most closely to an autosomal dominant pattern of inheritance, but there is also a more sporadic pattern of transmission, with occasional generations being phenotypically bypassed completely. It may be that this latter case represents a form of variable penetrance. In the remaining families, no clear other pattern of inheritance was seen. The heterogeneity of the inheritance patterns may also indicate polygenic transmission. Examples of pedigrees that we observed are shown in Figure 1.

Probability assessment. Continuous probability, based on LV size and percent FS at initial assessment, may be determined by comparing the distribution (10) of these variables in patients with DCM at presentation versus that in people with normal variables at initial screening. Both of these groups of data are normally distributed, and the probability thus calculated refers to any individual measurement belonging to one or the other distribution. We calculated these probabilities for a range of LV diameters and similarly for a range of FS values and show the results as the probability curves in Figure 2A.

On retrospective assessment, relatives with LVE tend to have a higher rating on the probability curve than do normal

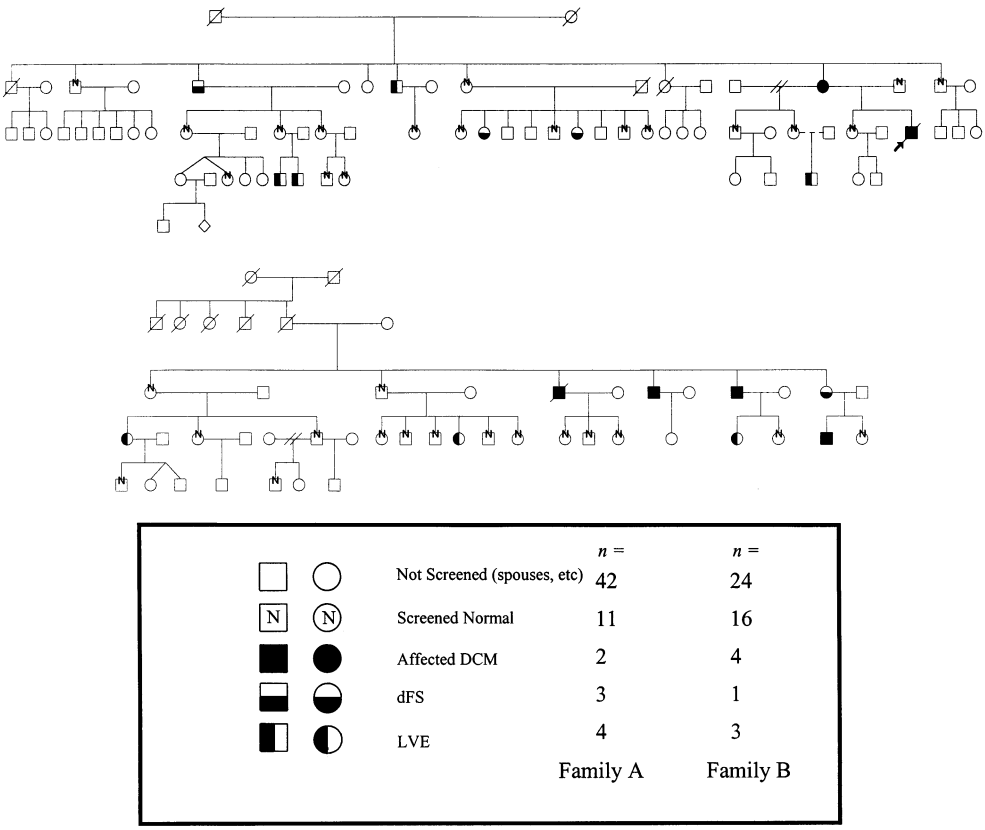


Figure 1. Typical pedigrees in relatives with DCM, LVE and dFS. **Top pedigree**, Family A; **bottom pedigree**, Family B.

relatives. An obvious limitation of this type of analysis is that the two observed echocardiographic dimensions may be abnormal for many reasons other than DCM; for example, ischemic cardiac enlargement would result also in a high probability score on our curve. Therefore, these curves are a guide only for patients in whom other causes of LVE can be excluded. Combining the individual probabilities shown in Figure 2A allows more accurate assessment of individual probability; the combination curves are shown in Figure 2B.

Discussion

Few data and no definitions exist to identify early disease in familial DCM. In the present study, asymptomatic echocardiographic abnormalities were seen in 29% of relatives. The most common abnormality was LVE. The association of other abnormalities (clinical, metabolic and ECG) with LVE suggests that it is not simply a "variant" of normality or a manifestation of high physical fitness, as in the athletic heart syndrome. The present study also demonstrates that a proportion (27%) of relatives with LVE progress to symptomatic DCM; it is therefore likely that LVE itself represents an early stage in the disease process.

Depressed FS does not appear to share the same risk of progression to DCM; it may thus represent a limited manifestation rather than early disease.

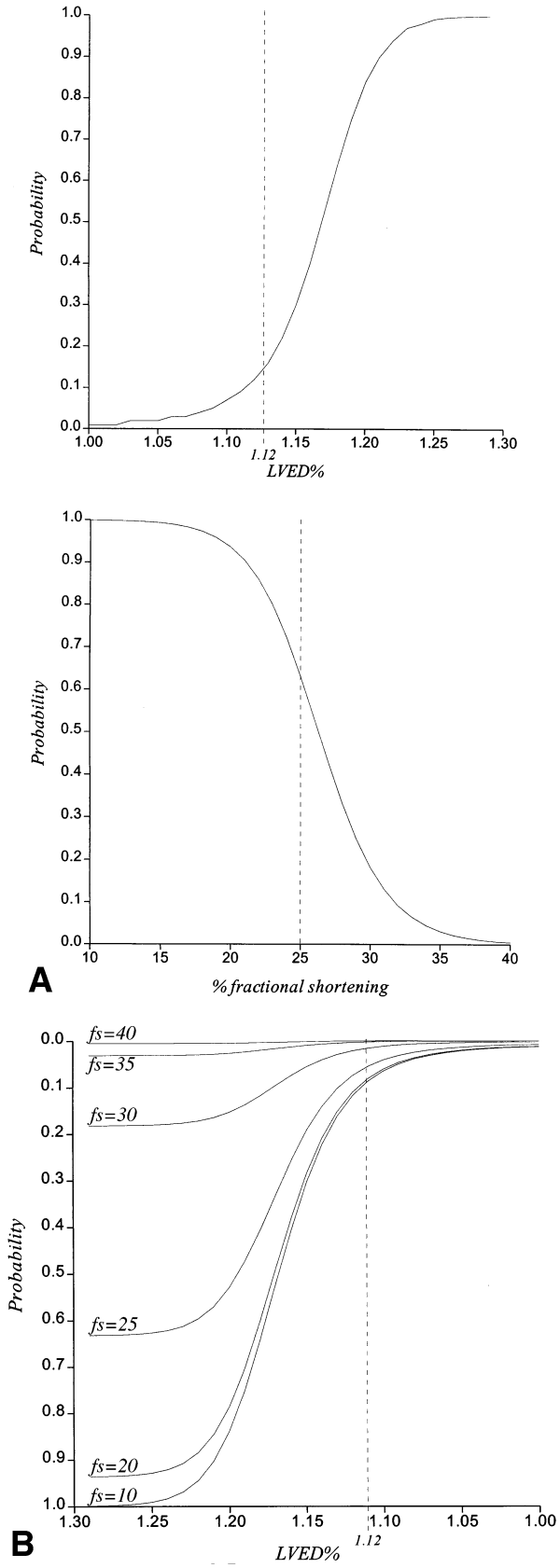
The present study determined that abnormalities of cardiac function are identifiable in asymptomatic relatives. Although not fulfilling conventional criteria for the diagnosis of DCM, the abnormalities in a subset of these people progress to the extent that conventional diagnostic criteria are achieved, and symptoms appear that lead to a number of disease complications, including sudden death.

It is therefore suggested that the assessment of risk in any individual relative must be based on the noninvasive investigations outlined in the present study. Echocardiography remains the most important of these investigations because LVEDD in LVE has a statistically significant predictive association with the development of DCM. The lack of symptoms in subjects with LVE does not necessarily indicate a good prognosis. Abnormalities on physical examination of the cardiovascular system are more frequent in relatives with LVE than in normal relatives; hence, although not specific, such abnormal signs on physical examination must be carefully sought.

Abnormalities on standard and high resolution electrocardiography or abnormal oxygen consumption on exercise testing does not have the predictive value of increased LVEDD on echocardiography. Nevertheless, these abnormalities are more common in relatives with LVE and should be assessed if facilities are available because the finding of such abnormalities will augment the individual likelihood of any person with LVE being at risk for disease progression.

Analysis of the combined probability curves (Fig. 2B) may

Figure 2. Probability of DCM according to **(A)** LVEDD% and percent FS and **(B)** combined LVEDD% and percent FS.



be used as a guide to individual risk in a relative with LVE. However, assessment of these curves suggests that our current definition of the upper limit for normal LV size (<112% of that predicted according to the formula of Henry et al. [7]) is considerably underestimated in the context of DCM. For future analyses, it appears that an upper cutoff of 118% would allow more frequent identification of at-risk subjects because this value infers a chance of ~50% that a relative with LVE will develop DCM in the presence of FS of 25% (Fig. 2B).

Whether subjects with LVE or dFS require therapeutic intervention remains to be determined because no specific treatment data exist for these groups. Data from the asymptomatic limbs of the Studies of Left Ventricular Dysfunction (SOLVD) (11) and Survival and Ventricular Enlargement (SAVE) (12) trials suggest that angiotensin-converting enzyme (ACE) inhibition is beneficial in people with asymptomatic LV dysfunction, and it is reasonable to assume that such benefits will extend to relatives with LVE. However, whether such treatment with ACE inhibition will alter the risk of disease progression remains unknown and is currently the subject of further study. Furthermore, if myocardial inflammation in the context of early disease can be conclusively proved, then intervention with immunosuppression or perhaps cytokine antagonists may become an appropriate additional therapy.

The identification of relatives with early DCM is important in establishing the true prevalence of familial disease; if the premise that a proportion of relatives with LVE will eventually develop DCM is correct, then current figures for the prevalence of familial disease (9% to 20%), and therefore for offspring risk, are considerably underestimated. This underestimation is supported by the findings of the present study, which showed that when LVE is included as evidence of early disease, the prevalence of familial disease rises to 48%.

Conclusions. Twenty-six percent of relatives of patients with DCM have asymptomatic LV enlargement or isolated dFS demonstrable on echocardiography. Other noninvasive investigation results are also abnormal in these subgroups. Prospective follow-up revealed that 27% of such initially asymptomatic subjects with LVE go on to develop DCM and may suffer the recognized complications of the condition.

We gratefully acknowledge the assistance of Karen Reardon, computer databasing; Vicky Murday, MD, Department of Medical Genetics; Sr. Carolanne Page and Sr. Mary Gould, clinical organization; Gill Smith and Sally Nunn, Senior Echocardiographers; and Michelle Leigh-Jones, Chief Cardiac Technician, in the completion of this study.

References

1. Brandenburg RO, Chazov E, Cherian G, et al. Report of the WHO/ISFC task force on definition and classification of the cardiomyopathies. Circulation 1981;64:1397–9.
2. Yamada T, Fukunami M, Ohmori M, et al. New approach to the estimation of the extent of myocardial fibrosis in patients with dilated cardiomyopathy: use of signal-averaged electrocardiography. Am Heart J 1993;126:626–31.
3. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen

uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol 1996;27:345–52.

4. Van den Broek SA, Van Veldhuisen DA, De Graeff PA, Landsman ML, Hillege H, Lie KI. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1992;70:359–63.
5. Kelly DP, Strauss AW. Inherited cardiomyopathies. N Engl J Med 1994;330: 913–9.
6. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992;326:77–82.
7. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation 1980;62:1054–61.
8. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two dimensional echocardiographic study. J Am Coll Cardiol 1983;2:437–44.
9. Blackie SP, Fairbarn MS, McElvaney GN, Morrison NJ, Wilcox PG, Pardy RL. Prediction of maximal oxygen uptake and power during cycle ergometry in subjects older than 55 years of age. Am Rev Respir Dis 1989;139:1424–9.
10. Dennis NR, Carter CO. Use of overlapping normal distributions in genetic counselling. J Med Genet 1978;15:106–8.
11. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions: the SOLVD Investigators [published erratum appears in N Engl J Med 1992; 327:1768]. N Engl J Med 1992;327:685–91.
12. Pfeffer MA, Braunwald E, Moye LA, et al., for the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. N Engl J Med 1992;327:669–77.