

Right ventricular dysplasia: a clinical and pathological study of two families with left ventricular involvement

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Abstract

Background—Right ventricular dysplasia is a heart muscle disease of unknown cause that is often familial and is anatomically characterised by adipose or fibroadipose infiltration of the right ventricular myocardium. It is generally regarded as a selective disorder of the right ventricle.

Aim—To investigate the prevalence and characteristics of left ventricular involvement in two families in which at least one member had right ventricular dysplasia confirmed at necropsy.

Methods and results—Eight patients were found to be affected by right ventricular dysplasia. In three of them this was confirmed at necropsy. Echocardiography or angiography or both showed left ventricular involvement in seven. This ranged from localised wall motion abnormalities to moderate or severe left ventricular dysfunction. The disease was progressive in four cases. At necropsy the left ventricular myocardium showed predominant fibrosis and degenerative changes of the myocardial cells. There were areas of myocardial thinning with fatty infiltration at the apex in two patients.

Conclusions—Familial right ventricular dysplasia can be a progressive disorder that affects the left ventricle. Advanced disease may be clinically confused with dilated cardiomyopathy.

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Right ventricular dysplasia, a disease that selectively affects the right ventricle,¹ is anatomically characterised by adipose or fibroadipose infiltration of the myocardium.^{1,2} These changes account for the electrical instability and the frequent ventricular arrhythmias³ that are a not an uncommon cause of sudden death.⁴ In some cases of right ventricular dysplasia the left ventricle was also affected.⁵⁻¹⁹ The frequency, characteristics, and severity of this involvement, however, are still unknown, as is the aetiology of the disease.²⁰

A familial occurrence has been reported by several groups^{1,21-26} and recently Nava *et al* suggested that the disease is a genetic condition

with autosomal dominance and variable expression and penetrance.²⁷

We report findings in two families in which at least one member had clear postmortem evidence of right ventricular dysplasia. The study of these families showed (a) the familial nature of the disease; (b) the presence and characteristics of an important left ventricular involvement; and (c) the progression of the disease.

Case reports

FAMILY A

Case 1 (proband)—This patient started to experience palpitation at the age of 17 when a chest x ray showed an enlarged heart. When she was 36 she began to notice dyspnoea on exertion and 18 years later she had a left hemiparesis. In the same year she was admitted to our department in heart failure.

Third and fourth heart sounds and systolic murmurs caused by mitral and tricuspid regurgitation were present on clinical examination. The standard electrocardiogram showed transient first degree atrioventricular block, left anterior hemiblock, and multiform ventricular extrasystoles with left and right bundle branch block configurations. A chest x ray showed considerable cardiomegaly. The M mode echocardiogram showed left ventricular enlargement with poor systolic function (left ventricular end diastolic diameter (LVEDD) 6 cm, fractional shortening (FS) 8%). Cardiac catheterisation showed a slightly enlarged left ventricle (end diastolic volume index, 132 ml/m²) with a low left ventricular ejection fraction (0.29). Pressure measurements were within normal limits. The coronary arteries were normal.

Treatment with digoxin and diuretics improved the symptoms. Two years later she developed an advanced atrioventricular block that required cardiac pacing. Her clinical condition progressively deteriorated and she died at the age of 58.

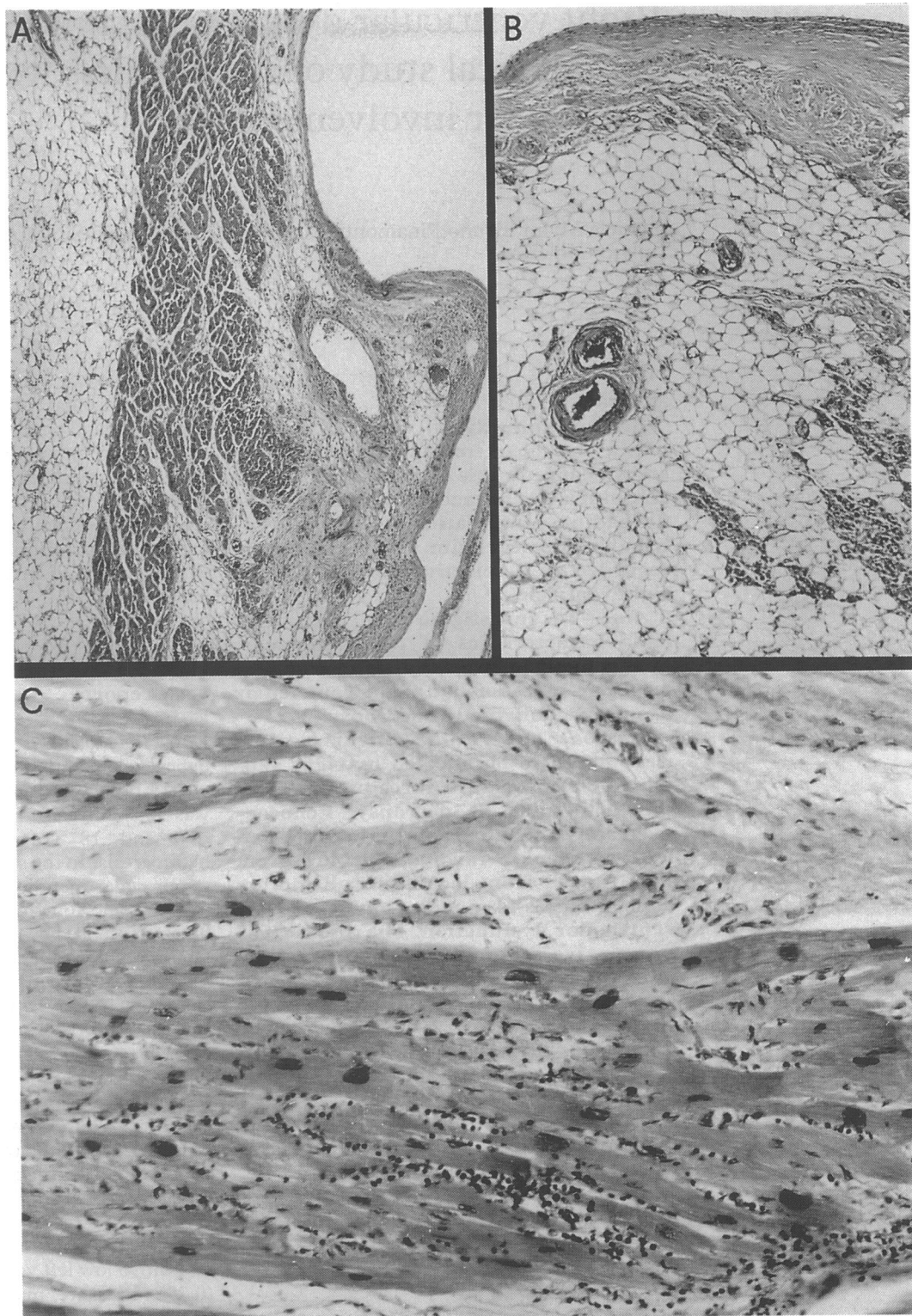
At necropsy all the cardiac chambers were grossly enlarged (weight of the heart 720 g). The coronary arteries were normal. The left ventricular wall was 7 mm thick whereas the walls of the right ventricle were very thin (1 mm) and massively infiltrated by fatty and fibrous tissue: only a few myofibres remained in the subendocardial layer (fig 1A). There were

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Figure 1 (A) Histological sections from patient 1 (family A) showing atrophy of the cardiac myocytes, fatty infiltration, and subendocardial fibrosis in the right ventricle (haematoxylin and eosin; original magnification, $\times 12.5$); (B) massive fatty infiltration of the myocardium and thickening of the endocardium of the right ventricle (haematoxylin and eosin; original magnification, $\times 40$); and (C) attenuation of the cardiac myocytes; interstitial inflammatory mononuclear infiltrates and fibrosis in the left ventricle (haematoxylin and eosin; original magnification, $\times 40$).



some irregular scars in the left ventricular wall. At histological examination the right ventricular specimens showed diffuse and considerable fatty infiltration, with the remaining cells being hypertrophied and attenuated (fig 1A and B). There was an interstitial inflammatory infiltrate and severe fibrosis in the left ventricle (fig 1C).

Case 2 (the proband's eldest son) had a first episode of sustained ventricular tachycardia when he was 19. He continued to have palpitation. When he was 33 clinical findings were normal, but there were low voltage, abnormal

QS traces in leads II and III and aVF and negative T waves in V5–V6. The M mode and cross sectional echocardiograms showed dilatation and diffuse hypokinesia of the left ventricle (LVEDD 6.5 cm, FS 15%) (fig 2); the right ventricle showed multiple akinetic areas (fig 3) and diffuse hypokinesia. Cardiac catheterisation showed that left ventricular end diastolic pressure was somewhat increased (14 mm Hg), while left ventriculography showed an enlarged left ventricle (end diastolic volume index = 154 ml/m²) with a reduced ejection fraction (0.35). Three endomyocardial biopsy

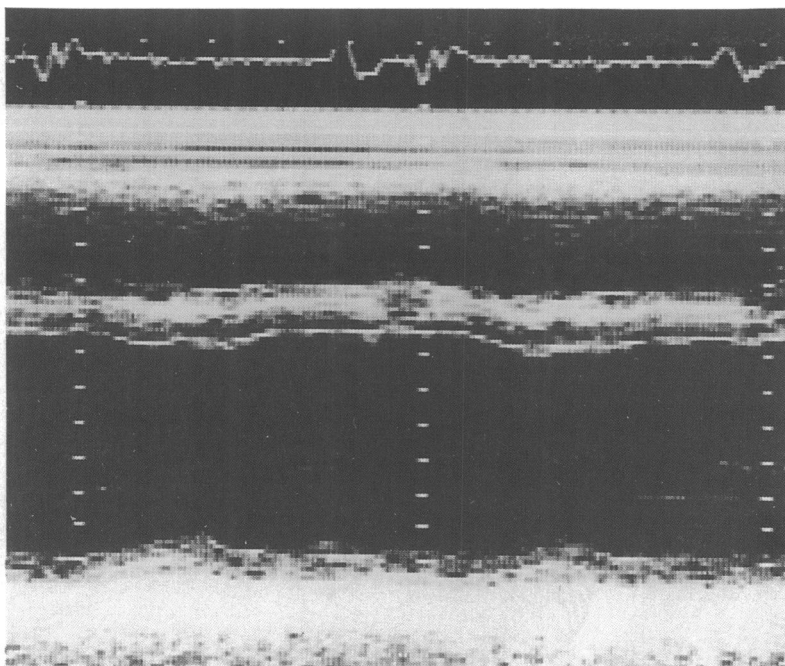


Figure 2 M mode echocardiogram of the left ventricle in patient 2 (family A) showing a moderate increase in end diastolic diameter (6.5 cm) and hypokinesis of the interventricular septum and the posterior wall of left ventricle. Left ventricular fractional shortening is 15%.

specimens from the right ventricle showed focal hypertrophy and attenuation of the myocytes, considerable interstitial fibrosis, and focal fatty replacement.

In the same year he was admitted with sustained ventricular tachycardia with a right bundle branch block configuration. In addition Holter monitoring showed non-sustained ventricular tachycardias with a left bundle branch block configuration. The arrhythmias were controlled by amiodarone and β blockers. When he was 37 left and right heart failure

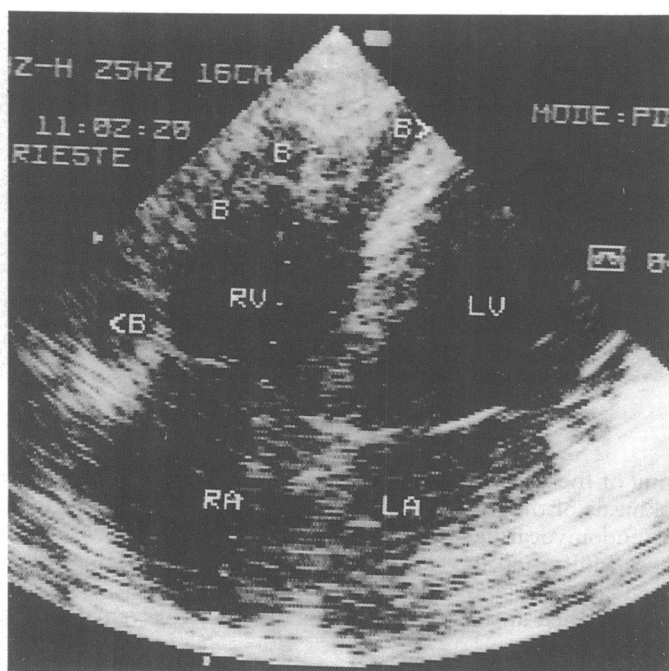


Figure 3 Cross sectional echocardiogram (patient 2, family A) (modified apical four chamber view, systolic frame) showing a grossly enlarged right ventricle (RV) with multiple akinetic bulges (B) in the lateral wall and at the apex. Right ventricular function was severely depressed. The right atrium (RA) is dilated. LV, left ventricle; LA, left atrium.

developed. This was successfully treated with digoxin, diuretics, and enalapril.

Case 3 The proband's second son had episodes of ventricular tachycardia when he was 15. Clinical examination was normal except for a systolic lift in the left parasternal area and a wide splitting of the second heart sound. The chest x ray was normal. The electrocardiogram showed low voltage QRS complex, high voltage R waves in V1 and V2, and negative T waves from V1–V4. Non-sustained ventricular tachycardia of left bundle branch configuration was occasionally seen. A M mode echocardiogram showed a dilatation of the right ventricle (EDD = 3.1 cm) with a normal left ventricle.

During the follow up he remained symptom-free but an echocardiogram showed a progressive reduction of left ventricular function (fractional shortening decreased from 40% to 25%) and multiform ventricular extrasystoles were detected on ambulatory monitoring. He died suddenly at the age of 22.

At necropsy the heart weighed 400 g and all the chambers were dilated. The coronary arteries were normal. The left ventricular wall was 10 mm thick, whereas the walls of the right ventricular outflow tract and of the posterior wall were less than 1 mm thick and sometimes contained only few myocardial fibres surrounded by fibrous tissue (fig 4). Furthermore there was irregular scarring in the subendocardial and in the subepicardial layers of the left ventricle.

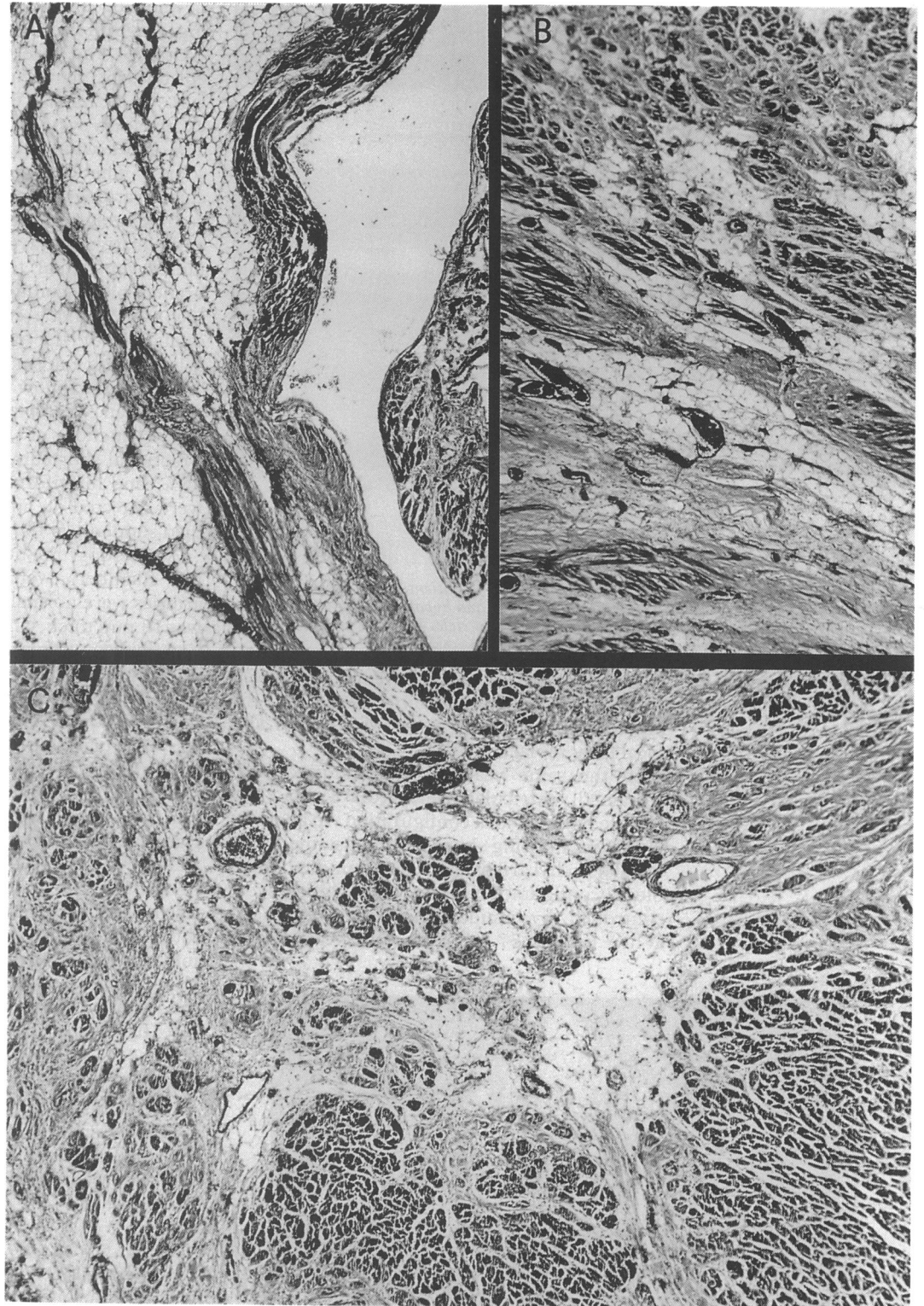
Histological examination showed that the right ventricular free wall was extensively infiltrated by fatty and fibrous tissue (fig 4A). The myocardial fibres of both ventricles were attenuated and hypertrophied and the endocardium was slightly thickened. Areas of fatty infiltration and severe interstitial scarring were also present at the left ventricular apex and in the septum; there were more evident in its right side (fig 4B and C).

FAMILY B

In this family five patients had right ventricular dysplasia and in four this involved the left ventricle. Figure 5B shows the pedigree of this family and the table summarises the clinical findings.

Case 1 (proband)—Effort pain in the hepatic region developed in a 51 year old woman. Mitral regurgitation and tricuspid regurgitation were found on clinical examination. The electrocardiogram showed atrial fibrillation and negative T waves in leads VI–V4. Echocardiographic and angiographic data showed important right ventricular dysfunction with a slightly dilated left ventricle that had normal pump function. As heart failure progressed hepatomegaly and ascites developed. Moreover, an advanced atrioventricular block developed which required endocardial pacing and she had episodes of sustained ventricular tachycardia with a left bundle branch block configuration. Echocardiography and cardiac catheterisation were repeated and showed severe dilatation and hypokinesia of the right

Figure 4 Histological sections from patient 3 (family A) showing (A) widespread myocardial fatty infiltration of the right ventricle and extreme atrophy of the remaining myocardial cells (haematoxylin and eosin; original magnification, $\times 12.5$). Sections of the left ventricle near (B) the apex and (C) the interventricular septum (posterior third) showing interstitial fatty infiltration and fibrosis (haematoxylin and eosin; original magnification, $\times 12.5$).



ventricle, with akinetic bulging of the walls at several sites and apical hypokinesis of the left ventricle. Right ventricular endomyocardial biopsy showed massive adipose infiltration in one specimen and interstitial fibrosis and hypertrophy in the other two. She died at the age of 62 in congestive heart failure.

Histopathological examination showed that the right ventricular wall was massively infiltrated by adipose and fibrous tissue (fig 6A). A few myocardial cells were present, mostly within the trabeculae. The left ventricular

myocardium showed hypertrophy and attenuation of myocytes with slight interstitial fibrosis and endocardial thickening (fig 6B). There was a zone of fatty and fibrous infiltration with decrease of myocardial cells at the left ventricular apex near the interventricular septum.

Case 2 (proband's brother)—This patient had a cardiological evaluation when he was 49 because of cardiomegaly at chest x ray; at that time clinical examination, electrocardiography, and M mode echocardiography were normal.

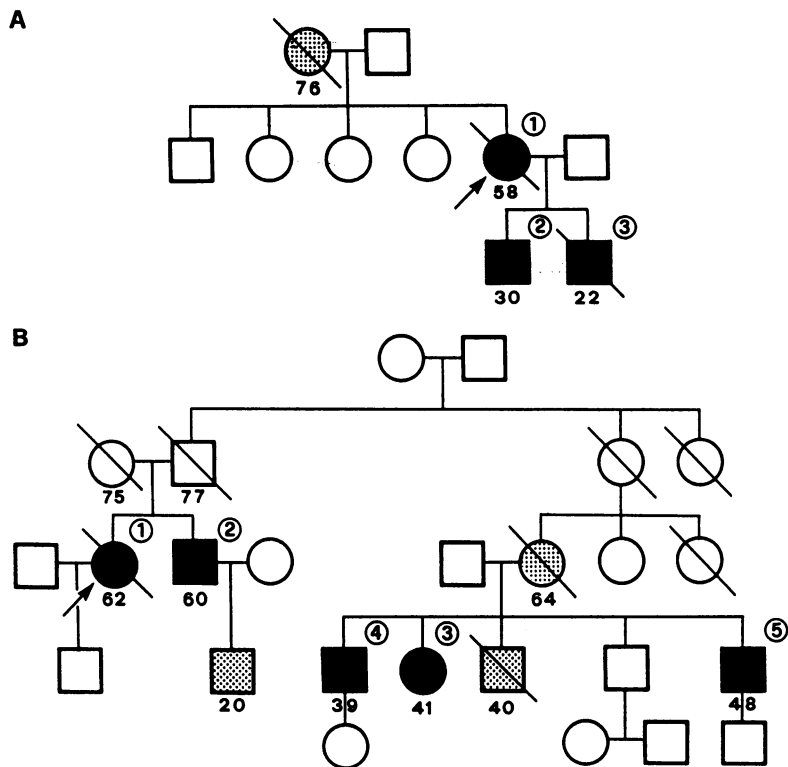


Figure 5 Pedigree of the two families showing mode of inheritance of right ventricular dysplasia. Ages at diagnosis or death are shown (slashed lines). Numbers inside circles indicate cases. Solid squares (males) and circles (female) indicate confirmed cases. Stippled squares and circles indicate suspected cases. Arrows indicate probands.

The patient was symptom free until he was 56 when he was admitted to hospital because of presyncope caused by sustained ventricular tachycardia with a left bundle branch block configuration. Two years later congestive heart failure developed. Atrial fibrillation was present, while M mode and cross sectional echocardiography showed a dilated right ventricle with akinetic bulges and a reduced left ventricular ejection fraction. A left ventricular endomyocardial biopsy specimen showed hypertrophy and interstitial fibrosis. The

endocardium was moderately thickened by fibrosis.

Right ventricular biopsy specimens showed mild hypertrophy and interstitial fibrosis. One specimen was infiltrated by adipose tissue.

Case 3 (proband's cousin)—Congestive heart failure developed when this woman was 36, and severe mitral regurgitation was diagnosed and successfully treated with surgical repair. Two years later she fainted because of atrial fibrillation with advanced atrioventricular block. This was treated by endocardial pacing. She did not recover completely: heart failure recurred and cross sectional echocardiography showed a dilated right ventricle with bulging into the outflow tract, depressed systolic function, and hypokinesis of the left ventricular apex.

Case 4 At 29 a chest x ray showed cardiomegaly and the electrocardiogram showed epsilon potentials and inverted T waves in the anterior precordial leads. Ten years later echocardiography and angiography showed the presence of a dilated right ventricle with a dyskinetic outflow tract and bulging of the apex and the lateral and diaphragmatic walls. The left ventricle was normal. Right ventricular dysplasia was diagnosed. This patient had an episode of sustained ventricular tachycardia with left bundle branch block configuration treated with DC countershock. He remains symptom free on antiarrhythmic therapy.

Case 5 was symptom free but an echocardiogram showed a dilated right ventricle with akinetic bulges in the anterior and inferior walls. The left ventricle was slightly dilated with hypokinesis of the posterior wall and normal pump function.

Discussion

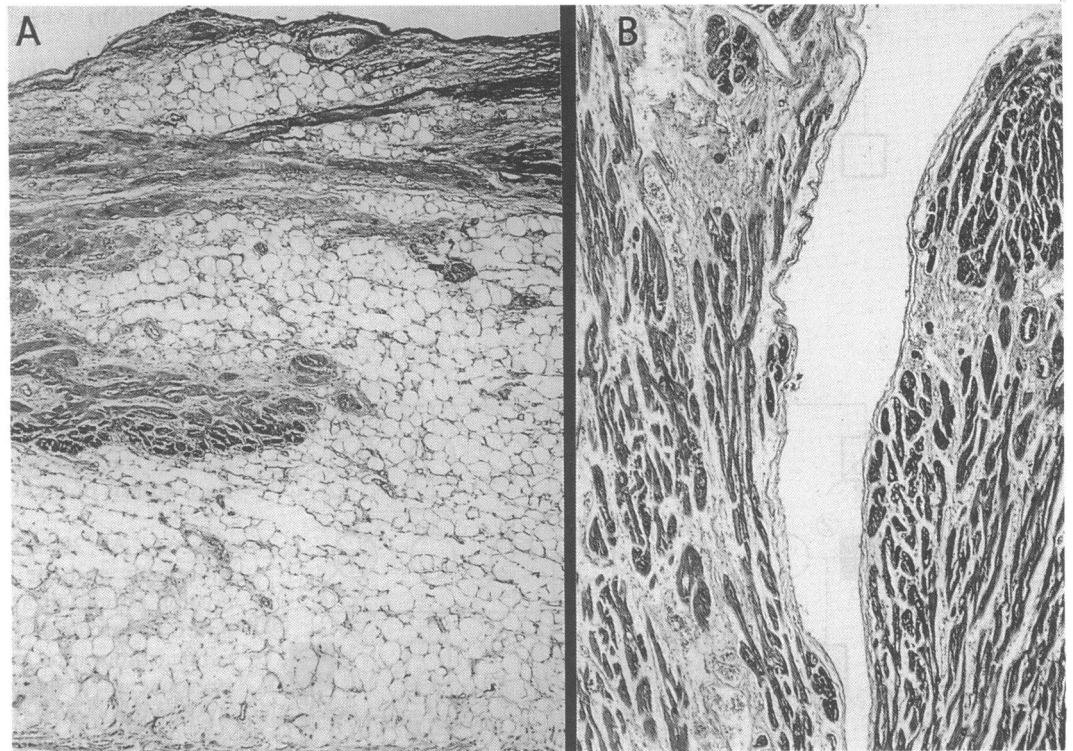
Right ventricular dysplasia is a myocardial disorder in which the walls of the right ventri-

Clinical and pathologic findings in family B

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	F	M	F	M	M
Age at diagnosis (yr)	53	60	41	39	48
Clinical history	Right heart failure (since the age of 51) S3-S4 MR and TR	Presyncope (due to VT)	Dyspnoea	Syncope (due to VT)	Symptom free
Clinical history	S3-S4 MR and TR	N	MR (treated with valvuloplasty) SR-> AF-> AVB	Split P2	S4
ECG/Holter	AF, AVB VT(LBBB configuration)	AF-VT (LBBB configuration)		EP-VT (LBBB configuration)	EP, VE couplets
Echocardiography					
LVEDD-LVESD (cm)	4.7-3	5.6-4.4	6.2-4.2	5.1-3.7	5.9-4.6
FS%	36	21	32	27	22
RVEDD (cm)	4	2.2	2	4.6	2.7
RV*	Dilated and hypokinetic with akinetic bulges	Dilated with akinetic bulges	Dilated with dyskinetic outflow tract	Dilated with multiple wall bulges	Dilated with anterior and inferior akinetic bulges
LV*	Normal -> apex hypokinetic	Dilated and hypokinetic	Apex hypokinetic	Normal	Posterior wall hypokinetic
Haemodynamics:					
LV pressure (mm Hg)	110-0/10	160-0/20	110-0/20	88-0/11	
LVEDV (ml/m2)	110	124	104	100	
LVEF %	67	43	51	55	
Endomyocardial biopsy	Adipose infiltration, hypertrophy, interstitial fibrosis	Adipose infiltration, interstitial fibrosis, endocardial thickening	Adipose infiltration	Hypertrophy, endocardial fibrosis	

AF, atrial fibrillation; AVB, atrioventricular block; EP, epsilon potentials; FS, fractional shortening; LBBB, left bundle branch block; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; p, pulmonary sound; RV, right ventricle; RVEDD, right ventricular end diastolic diameter; S3, third sound; S4, fourth sound; SR, sinus rhythm; TR, tricuspid regurgitation; VE, ventricular extrasystoles; VT, ventricular tachycardia.
*Cross sectional.

Figure 6 Histological sections in patient 1 (family B) showing (A) adipose tissue extensively infiltrating the myocardium throughout its entire thickness in the right ventricle (haematoxylin and eosin; original magnification $\times 12.5$) and (B) areas of interstitial fibrosis in the subendocardial region of the left ventricle (haematoxylin and eosin; original magnification, $\times 16$).



cle are infiltrated by adipose or fibroadipose tissue. Some workers prefer the term “right ventricular cardiomyopathy” because the aetiology of the disease is not known.^{2 4 26 28} Fontaine *et al*, however, suggested that in some cases right ventricular dysplasia may be a consequence of a previous myocarditis.²⁰ Certainly, at necropsy the right ventricle of one of our patients (patient 1, family A) showed considerable adipose infiltration while inflammatory cells were present in the left ventricular wall. Several reports of the familial occurrence of right ventricular dysplasia^{1 21 26} suggested a genetic basis to the disease, and an autosomal mode of inheritance with variable expression and penetrance was postulated.^{26 27} The analysis of the two pedigrees in our study confirmed that in both families right ventricular dysplasia was probably an autosomal dominant trait.

Others have reported left ventricular involvement in right ventricular dysplasia.⁵⁻¹⁹ Left ventricular abnormalities may be localised (asynnergic areas, often in the inferior wall and the apex)^{1-9 12 13 17 19} or diffuse (diffuse moderate hypokinesia).^{16 17 19} Sometimes the left ventricle seems to be morphologically normal at rest, but Manyari *et al* used radionuclide angiography to show an inadequate increase in of ejection fraction during exercise, which indicated latent left ventricular dysfunction.¹⁰ Histological examination of the left ventricle usually shows non-specific changes: areas of severe myocardial atrophy with adipose or fibroadipose infiltration are rarely found.⁸

There are a limited number of studies of familial cases of right ventricular dysplasia with necropsy confirmation.^{13 23 24} In families in which several members were affected, pathological changes of the left ventricle were more common^{13 24} and sometimes more severe.¹³

We found clear post-mortem evidence of right ventricular dysplasia with left ventricular involvement in three members of two families. While the right ventricle had typical changes, characterised by extensive fatty infiltration of the myocardium, the abnormalities in the left ventricle varied and were not always typical. Adipose tissue was found only in the region of the apex or in the septum in two cases (case 3, family A and case 1, family B) whereas interstitial fibrosis of different degrees was always present. Clinical involvement of the left ventricle ranged from mild localised abnormalities of the left ventricular wall (cases 1, 3, and 5 in family B) to a moderate or severe reduction of systolic function (cases 1 and 2 in family A). In at least four of these cases (cases 2 and 3 in family A and cases 2 and 3 in family B) left heart failure was present suggesting a clinical diagnosis of dilated cardiomyopathy.

In some cases right ventricular dysplasia is a progressive disease with left ventricular involvement, which may appear relatively late.^{11 13 14 19 29} This pattern was observed in some of our cases (the second son in family A and the proband and brother in family B).

We found that in some individuals with familial right ventricular dysplasia both the left and right ventricles were affected. Our clinical data were strongly supported by post-mortem examination performed in three cases from two families. We confirm the familial background of the disease,²¹⁻²⁷ which can progress toward heart failure and in some cases may be confused with dilated cardiomyopathy.

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