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Familial dilated (congestive) cardiomyopathy

Occurrence in two brothers and an overview of the literature

J. Z. PRZYBOJEWSKI, J. J. VAN DER WALT, P. J. VAN EEDEN, F. A. C. TIEDT

Summary

Two young White brothers had dilated (congestive) cardiomyopathy. The elder came to autopsy after a chronic course of congestive cardiac failure; the younger underwent repeated cardiac catheterization and transvenous right ventricular endomyocardial biopsy specimens demonstrated histopathological features in keeping with a diagnosis of idiopathic dilated cardiomyopathy. These brothers may have the familial form of the disease, although post-viral myocarditis cardiomyopathy cannot be entirely excluded. The literature relating to familial dilated (congestive) cardiomyopathy is reviewed.

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Case presentations

Case 1

This 24-year-old White man was apparently very healthy until July 1981 when he suffered a bad bout of influenza. Some 2 months later he had a pulse rate of 140/min as well as a loud third heart sound on auscultation. He denied having any symptoms but was advised not to exert himself in view of a possible diagnosis of viral myocarditis. An electrocardiogram (ECG) was normal apart from sinus tachycardia. A chest radiograph revealed no cardiomegaly, but the heart was described as 'globular'. The consulting physician decided to treat him with digoxin 0,25 mg/d. A significant fact in the history was that the patient's elder brother had died of dilated (congestive) cardiomyopathy at the age of 25 years after having presumed 'viral myocarditis' (see 'Case 2' below). What may also be of significance is that his mother, who had been taking long-term oral contraceptives, had experienced a sudden episode of chest pain which led to her death; this may have been due to acute pulmonary embolism or acute myocardial infarction.

In view of the possibility of a post-myocarditis dilated (congestive) cardiomyopathy, his physician referred him to the Cardiac Clinic at Tygerberg Hospital, and he was admitted on 20 September 1981. Physical examination revealed few abnormal features apart from slight left ventricular cardiomegaly and a soft third heart sound. Side-room test results were normal, as were the results of serum chemical and haematological investigations. The resting 12-lead ECG was unremarkable apart from a significant sinus tachycardia. The chest radiograph delineated a globular heart with borderline cardiomegaly, but the lung fields were normal. M-mode echocardiography showed features of decreased myocardial contractility as exemplified by a reduced ejection fraction of 31% (normal >55%), a shortening fraction of 15% (normal 28 - 38%) and a velocity of circumferential shortening of 0,64 (normal 1,15 - 1,35). There were no features of hypertrophic cardiomyopathy. The dimensions of the left ventricle were at the upper limits of normal (left ventricular end-diastolic diameter 55 mm (normal 35-56 mm), end-systolic diameter 47 mm). The right ventricle was not dilated.

A gated blood pool scan (using technetium-99m pyrophosphate) revealed a low left ventricular ejection fraction of 36% and some thickening of the left ventricular wall. Furthermore, there was a global decrease in left ventricular contractility in the presence of a normally contracting right ventricle. Cardiac catheterization showed features of mild pulmonary hypertension and borderline left ventricular failure (Tables I and II). Left ventricular cine angiography delineated moderately severe generalized hypokinesia, mild (non-calcific) mitral insufficiency and no evidence of mural thrombus formation. Aortic cine angiography demonstrated a normal aortic valve and arch.

Investigation thus established a diagnosis of dilated (congestive) cardiomyopathy which was not considered to be severe

Department of Anatomical Pathology and Cardiac Unit, Department of Internal Medicine, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP
J. Z. PRZYBOJEWSKI, M.B. CH.B., F.C.P. (S.A.)
J. J. VAN DER WALT, M.MED. (PATH.), M.D.
F. A. C. TIEDT, A.S.M.L.T.
1602-1603 Oasim North, Havelock Street, Port Elizabeth
P. J. VAN EEDEN, M.B. CH.B., B.SC. HONS, M.MED. (INT.), F.C.P. (S.A.)

TABLE I. INTRACARDIAC PRESSURES

Catheter position	Pressures (mmHg) 21 Sept. 1981	25 Nov. 1982	Comment
Right atrium	**'a' wave, 9 'v' wave, 5 (mean 3)**	**'a' wave, 13 'v' wave, 10 (mean 9)**	**Slightly elevated (25 Nov. 82)**
Right ventricle	**34/0-5**	**54/6-10**	**Raised pressures (25 Nov. 82)**
Main pulmonary artery	**34/16 (mean 22)**	**54/28 (mean 40)**	**Moderate pulmonary hypertension (25 Nov. 82)**
Ascending aorta	**102/78 (mean 90)**	**120/90 (mean 96)**	**Normal**
Left ventricle	**102/9-25**	**120/9-37**	**Markedly raised end-diastolic pressure**
Dp/dt (mm/s)	**1 829**	**1 778**	**Normal**
Pulmonary capillary wedge	**'a' wave, 25 'v' wave, 18 (mean 15)**	**'a' wave, 46 'v' wave, 40 (mean 35)**	**Very raised (especially on 25 Nov. 82)**

Dp/dt = left ventricular stroke work.

TABLE II. HAEMODYNAMIC DATA

Parameter	21 Sept. 1981	25 Nov. 1982
Oxygen consumption (ml/min)	**200**	**260**
Arteriovenous O_2 difference (mmol/l)	**1,60**	**2,05**
Cardiac output (Fick) (l/min)	**5,5**	**5,6**
Cardiac index (Fick) (l/min/m²)	**3,0**	**3,1**
Pulmonary vascular resistance (U)	**1,3**	**0,9**
Systemic vascular resistance (U)	**15,8**	**15,5**
Pulmonary/systemic resistance ratio (%)	**8,0**	**6,0**

enough to justify such drastic intervention as a cardiac transplantation. The patient was discharged from hospital and given digoxin therapy, and was followed up regularly by his private physician in Port Elizabeth.

Early in November 1982 he no longer had sinus tachycardia but began experiencing episodic fast atrial fibrillation and paroxysmal atrial tachycardia. He was then started on treatment with verapamil 40 mg 3 times daily with good effect. At this stage the patient denied experiencing any symptoms and was still most active, but the appearance of the supraventricular arrhythmias caused his physician again to refer him to the Cardiac Clinic, specifically for performance of endomyocardial biopsy and investigations to determine his haemodynamic status and suitability for cardiac transplantation. After readmission on 24 November 1982 examination revealed little change from his condition 1 year previously. Again results of side-room investigations and serum biochemical studies were within normal limits, as were haematological parameters. A resting 12-lead ECG demonstrated sinus rhythm of 105/min, a P-R interval of 0,18 second, mean QRS axis of 100°, left atrial hypertrophy and diffuse, nonspecific ST-T wave changes. Chest radiography showed no changes in the cardiac silhouette and the lung fields appeared normal. Gated blood pool scanning delineated generalized cardiomegaly, decreased biventricular contractility and a slightly reduced left ventricular ejection fraction of 48%, an improvement on the ventricular function as assessed in September 1981.

Cardiac catheterization was undertaken to reassess ventricular function and obtain endomyocardial biopsy specimens. Tables I and II reveal a significant deterioration in biventricular failure despite unchanged cardiac output. Left ventricular cine angiography demonstrated a more severe degree of generalized hypokinesia with mild mitral insufficiency (Fig. 1). Right ventricular cine angiography delineated a dilated and poorly contracting chamber. Multiple right ventricular endomyocardial specimens showed no specific characteristics on electron microscopy; the most conspicuous features were mitochondriosis, nuclear enlargement, lipofuscin pigment (Fig. 2) and an apparent loss or degeneration of contractile elements in places (Fig. 3). These findings, although entirely nonspecific, were in keeping with a clinical diagnosis of dilated (congestive) cardiomyopathy.

The possibility of cardiac transplantation was discussed but it was decided that the patient's haemodynamic status was not severe enough to justify such a major procedure, particularly since he had been taking minimal medication. The patient was given prazosin 1 mg 3 times daily, digoxin 0,25 mg/d and a moderate dose of a diuretic. It was decided for several reasons not to use long-term anticoagulant therapy for the prevention of systemic emboli usually originating from left ventricular mural thrombi. He was then discharged, to be followed up closely at home and to undergo non-invasive determination of myocardial function again in the near future, in order to decide upon the timing of cardiac transplantation.

Case 2

This 21-year-old White university student had an early history of asthma in childhood, recurrent pyelitis in 1974 and a recent history of spastic colon. He was a moderate cigarette smoker and drinker. In July 1977 a bout of influenza was complicated by several episodes of acute bronchitis. In October 1977 he noticed the onset of intermittent abdominal pain aggravated by walking. Some 2 weeks later he became anorexic and nauseous and vomited on several occasions. In addition, he complained of a sore throat, fever and cough. His general

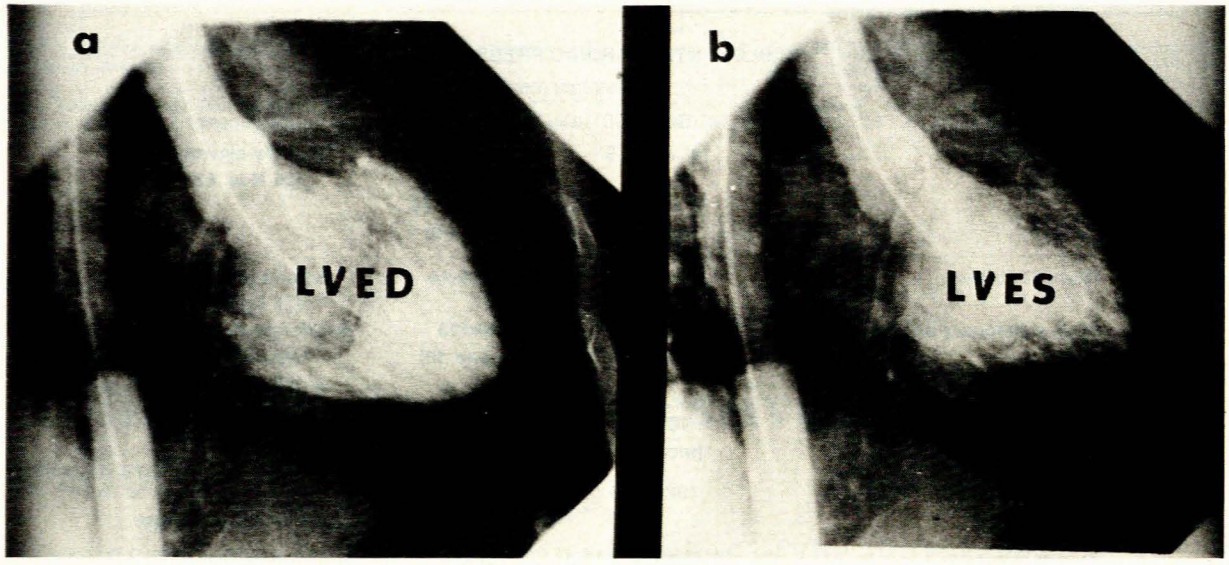

Fig. 1. Left ventricular cine angiograms in the right anterior oblique projection on 25 November 1982. More severe generalized hypokinesia than was evident on 21 September 1981 is visualized. There is still mild, non-calcific mitral insufficiency, but no features of a possible mural thrombus. a — LVED = left ventricle in end-diastole; b — LVES = left ventricle in end-systole.

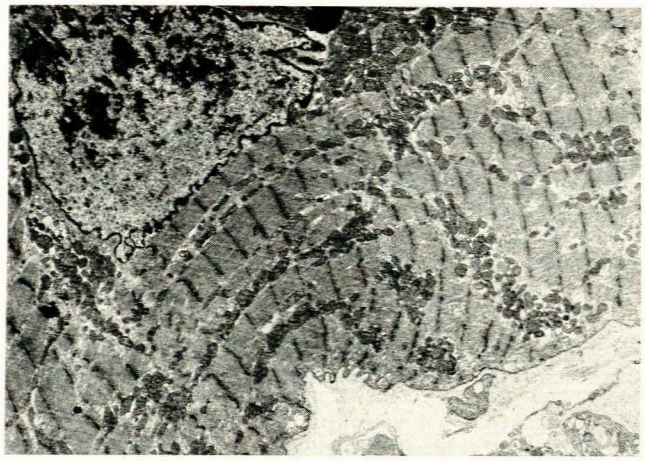

Fig. 2. Hypertrophied myocyte with enlarged nucleus, perinuclear lipofuscin and increase in mitochondria (x 7 300).

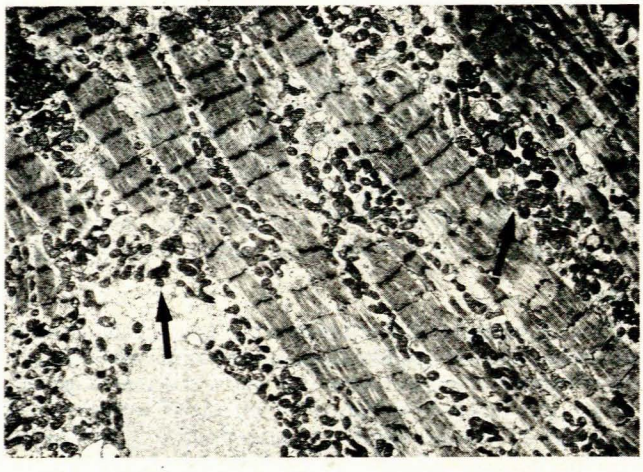

Fig. 3. Myocyte showing degenerative changes in mitochondria (arrows) and attenuation of myofibrils with an apparent loss of contractile elements (x 7 100).

practitioner diagnosed influenza. Nevertheless, a few days later he noticed swelling of his face, abdomen and ankles, as well as some shortness of breath on exercise and at rest. There was no history of joint pain or swelling, haematuria or oliguria, and he continued to be markedly nauseous.

He was admitted to the local hospital, where a physician examined him on 29 October 1977 and found him to be a very ill, apyrexial young man with marked tachycardia accompanied by 'slight paradoxus' and with a blood pressure of 120/100 mmHg. The jugular venous pressure was significantly elevated and there was extensive oedema of the face, sacrum and feet. Cardiomegaly with a marked protodiastolic gallop was noted; the fundi were normal. Further findings were those of extensive bilateral basal crepitations and a grossly enlarged and tender liver but no splenomegaly or jaundice. An ECG was stated to be 'non-contributory', and biventricular cardiac failure probably secondary to 'viral myocarditis' was diagnosed. The erythrocyte sedimentation rate was normal, and antinuclear factor and lupus erythematosus cells were both absent. The patient was confined to bed and given anti-cardiac failure medication and a course of steroid therapy, but he continued to have a tachycardia of 120/min and gallop rhythm, as well as poor peripheral circulation. Since there was no significant improvement he was admitted to the Provincial Hospital, Port Elizabeth, where cardiac catheterization was performed on 13 January 1978, some 6 months after the onset of his illness.

This investigation showed normal intracardiac pressures with 'no evidence of left ventricular failure', 'angiography did not show him to have poor myocardial function'. Further comment was that 'the left ventricular muscle appeared perhaps a little bit thickened, possibly due to oedema'. These findings caused the attending clinicians to take a more favourable view regarding prognosis.

The patient continued to display sinus tachycardia but of a milder degree. Towards the end of 1980 he suffered a further attack of influenza and was noted to be in 'flutter-fibrillation' for the first time in October 1980. His physician thought that this arrhythmia was caused by an overdose of digoxin, which was promptly discontinued for 1 week. However, the atrial fibrillation persisted and digoxin therapy was recommenced at a slightly reduced dosage. On 23 January 1981 the patient complained of anorexia, tiredness, swelling of the abdomen and tenderness of

the right hypochondrium; examination demonstrated no oedema, the blood pressure was 110/80 mmHg, and he was still in atrial fibrillation. His lungs were clear, but there was considerable non-tender hepatomegaly associated with possible early jaundice. Investigation failed to establish a possible diagnosis of infective hepatitis. The patient's condition continued to deteriorate with increasing cardiomegaly, and he was admitted to the Provincial Hospital, Port Elizabeth, on 14 March 1981. The atrial fibrillation was converted to rapid sinus rhythm and he was discharged after a week in hospital. During the ensuing few months he continued in biventricular cardiac failure, this necessitating readmission in June 1981. Cardiac transplantation was apparently discussed but the patient died within a few days of admission.

On macroscopic examination the heart showed generalized enlargement and weighed 470 g. Both ventricles were dilated, especially the left one. An antemortem thrombus was present in the left atrium. The heart valves were within normal limits and the coronary arteries were free of atheroma. On histological examination of the heart the myocytes showed obvious signs of hypertrophy, as indicated by the increase in cell size and the presence of bizarre enlarged nuclei. Many myocytes were attenuated and in cross-section appeared atrophic but contained enlarged hyperchromatic nuclei. The latter cells reflect the effect of chronic ventricular dilatation. The interstitium of the heart showed a fine, almost pericellular fibrosis of a very delicate nature (Fig. 4) but no inflammatory cells. The parietal endocardium of the left ventricle showed mild focal thickening due to fibro-elastosis (Fig. 5). Microscopy confirmed the presence of an organizing mural thrombus and the absence of any valvular lesion or significant coronary atherosclerosis. The histological features together with the clinical history and the gross appearance of the heart strongly suggested a diagnosis of idiopathic dilated ventricular cardiomyopathy. The severity of the congestive cardiac failure was reflected by the severe chronic passive congestion seen in the liver, spleen, kidneys and lungs.

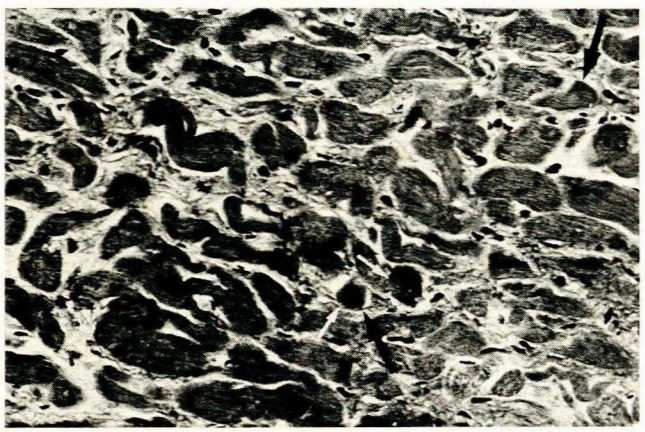

Fig. 4. Hypertrophied myocardial fibres. Note enlarged, hyperchromatic nuclei even in small fibres (arrows). **Delicate connective tissue separates the fibres (x 940).**

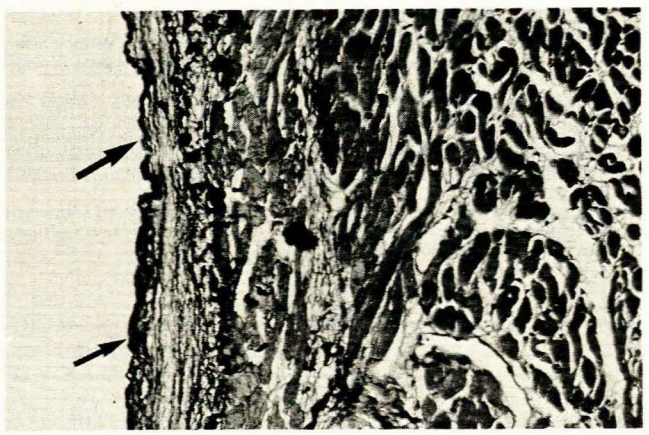

Fig. 5. Section from left ventricle showing mild endocardial fibroelastosis (arrows) **(x 470).**

Discussion

The aetiological factors involved in the pathogenesis of dilated (congestive) cardiomyopathy have occupied the thoughts of many researchers for several decades. Despite numerous publications, no satisfactory answer has emerged. As with many diseases, a hereditofamilial factor has been incriminated in an attempt to solve this most puzzling aspect of an exceptionally common and important disease (especially among Blacks) in Africa. The first report of familial cardiomyopathy, entitled 'Familial cardiomegaly', was that of Evans[1] in 1949, but it is not quite certain whether these cases were of the dilated (congestive) type or the hypertrophic variety. Similarly, authors such as Gaunt and Lecutier,[2] Bishop *et al.*,[3] Kariv *et al.*[4] and Emanuel *et al.*[5] were not quite clear in distinguishing between the dilated and hypertrophic forms of familial cardiomyopathy. This distinction is important since it has been well established that hypertrophic obstructive cardiomyopathy can be transmitted genetically. Nevertheless, the picture is somewhat clouded by the suggestion that the hypertrophic type can evolve into the dilated type. Anselmi *et al.*[6] described identical twin brothers who died suddenly; one had features of dilated cardiomyopathy whereas the other had those of hypertrophic cardiomyopathy. Coelho *et al.*[7] and Campbell and Turner-Warwick[8] also documented cases of 'familial cardiomyopathy', but again the histopathological features were not entirely clear. Further suggestions of a familial or hereditary pattern in dilated cardiomyopathy were published by Kariv *et al.*,[9] Pare *et al.*,[10] Biörck and Orinius,[11] Beasley,[12] Walther *et al.*,[13] Barry and Hall,[14] Garret *et al.*,[15] and Battersby and Glenner.[16] Most of these reports have suggested that the pattern of inheritance is by an autosomal dominant gene, and less frequently a recessive one.

The first report of a familial congestive cardiomyopathy in tropical Africa described twin brothers in Uganda.[17] However, Brink *et al.*[18] considered these cases probably to be coincidental since dilated (congestive) cardiomyopathy was so common in that part of Africa. These same authors[18] went on to describe the interesting condition of 'hereditary dysrhythmic congestive cardiomyopathy' in a White teenage girl who had repeated episodes of symptomatic ventricular tachycardia and fibrillation. Since the QTc was prolonged a left cervical ganglionectomy was performed, with limited success. Further follow-up revealed a progressively enlarging heart, and the girl died suddenly some 4 years later. Her elder brother had apparently died suddenly after effort but autopsy had not been performed. Ten generations of the family were traced and there was a strong history of sudden death. Furthermore, two young sisters, related through their parental branch to the above girl's family, were said to suffer from 'familial paroxysmal ventricular tachycardia'.[19]

Ross *et al.*[20] reported on what appears to be a similar (and unusual) disease to that documented by Brink *et al.*[18] They encountered the condition of 'idiopathic familial myocardiopathy' in families of three generations in which the inheritance pattern approached that of autosomal dominance. Some of the hearts displayed histological features resembling both idiopathic dilated myocardiopathy in adults and the idiopathic endocardial fibro-elastosis seen in children. Unusually extensive myocardial fibrosis was also encountered in some cases documented by Ross *et al.*,[20] a feature unusual in dilated cardiomyopathy and more commonly associated with severe coronary artery disease.

An unusual type of familial dilated (congestive) cardiomyopathy associated with hypogonadism and a unique collagenoma was described by Sacks *et al.*[21] in a 48-year-old White man, the proband, in whom severe tricuspid insufficiency was associated with significant right heart involvement and far less left heart involvement, a feature described in adults with 'right ventricular dysplasia'.[22]

The possibility of antecedent viral infection, particularly coxsackie B virus, in the two brothers described by us cannot be excluded with certainty. Viral myocarditis leading to dilated (congestive) cardiomyopathy has been strongly suggested by some workers.[23,24] Cambridge *et al.*[25] demonstrated a high level of antibodies against coxsackie B virus in the serum of patients whose illness commenced with a fever and lasted less than a year. In a large series of patients with idiopathic dilated cardiomyopathy Fuster *et al.*[26] found that about 20% had suffered a viral-type illness before presenting with cardiomyopathy. The onset of atrial fibrillation in both our patients caused haemodynamic deterioration and is usually a poor prognostic sign, occurring in some 15 - 20% of patients with this disease.[27–29] Immunological studies have also been carried out in cases of cardiomyopathy but no correlation between circulating antiheart antibodies and the type of cardiomyopathy was demonstrated.[30]

Recently, Factor and Sonnenblick[31] presented a challenging hypothesis incriminating a diffuse hyperactive myocardial microcirculation (microvascular spasm) in the pathophysiology of congestive cardiomyopathy. This, they say, rather than a primary disorder of heart muscle cells, is of prime importance and dictates the possible beneficial effects of treatment with calcium-antagonist drugs such as verapamil. Further work by Bristow *et al.*[32] and Willerson[33] demonstrated that ß-receptor density is diminished in congestive cardiac failure secondary to idiopathic dilated cardiomyopathy and 'ischaemic cardiomyopathy' (following previous myocardial infarction). This decrease, they claim, gives rise to decreased ß-adrenergic pathway sensitivity with subsequent diminished ß-agonist-stimulated myocardial contraction. Further research into dilated cardiomyopathy involved the use of thallium-201 scans after exercise. Some authors[34] have claimed that perfusion defects occur with ischaemic heart disease but not with idiopathic dilated cardiomyopathy. However, Dunn *et al.*[35] recently showed that this differentiation was unreliable.

Further management of the surviving brother described by us was made more difficult by the death of his older sibling. The parents have been exceptionally keen for him to undergo cardiac transplantation because they fear that he may also die. Nevertheless, he remains exeptionally well despite the obvious haemodynamic deterioration over a 1-year period (demonstrated by repeat cardiac catheterization). We do not believe that his present condition justifies the drastic intervention of heterotopic cardiac transplantation, and we will continue to follow him up closely on medical therapy in conjunction with his private specialist physician.

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