The course of idiopathic dilated cardiomyopathy in New Zealand

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SUMMARY The course of dilated cardiomyopathy in New Zealand was studied in 72 cases that were followed up for ≤10 years after cardiac catheterisation and coronary angiography. Eighty one per cent were male and 86% were white; the remainder were Maori. The mean age of patients at the time of investigation was 50-15 years. Most patients were unskilled labourers. The commonest presenting symptom was dyspnoea and the commonest physical sign was cardiomegaly. Mean survival time from first hospital presentation was 85 months; half the deaths were sudden. Factors predicting a poor survival included cardiomegaly, age, arrhythmias, cigarette smoking, and subclinical thiamine deficiency.

The syndrome of dilated cardiomyopathy in New Zealand appears to be identical with that seen in other European populations.

Dilated cardiomyopathy causes considerable mortality and morbidity throughout the world. Despite extensive investigations the aetiology and course of this condition remain incompletely understood. The most likely aetiological factors are a genetic defect or some environmental factor causing progressive myocardial cell damage. Evidence for a genetic defect is slim in the usually sporadic cases of this condition, whereas several environmental factors are associated with dilated cardiomyopathy. The most convincing evidence for an environmental aetiology comes from Keshan cardiomyopathy—a form of dilated cardiomyopathy endemic to the Keshan region of China. This has been causally linked with a deficiency of selenium. Sporadic reports from the United States also implicate selenium deficiency in the aetiology of dilated cardiomyopathy in non-Chinese populations. Links between the disease and other environmental factors are inconsistent.

There are few studies of the course of this disease. Most of these come from the United States or Europe. No long term studies have been done in New Zealand. For several reasons New Zealand is a natural experiment for the study of environmental influences in this disease. The population is mainly of Western European origin and New Zealand has the lowest soil content of selenium to which any European population is exposed. There is easy access to modern diagnosis and therapeutic facilities and the isolation of the country facilitates detailed long term follow up. A study of cardiomyopathy in such a setting may add to the understanding of this condition.

We report a 10 year prospective inquiry into the demographic, haemodynamic, and prognostic features of dilated cardiomyopathy as seen in New Zealand.

Patients and methods

Patients A prospective study of the course of dilated cardiomyopathy in New Zealand was started in 1974. All patients referred to one of us (HI) with cardiac failure of unknown aetiology were investigated by cardiac catheterisation and coronary angiography. Those in whom left ventricular ejection fraction was <50% and who did not have significant coronary artery disease (defined as 75% or greater cross-sec-
tional reduction of one or more major coronary vessels) were further investigated with a comprehensive protocol designed to establish aetiology of heart failure. Patients were excluded from the study if the investigations showed the presence of any agent known to cause cardiac muscle dysfunction—for example diabetes, hypertension, or collagen disorders. Those with rising titres of viral antibody were considered to have myocarditis and were also excluded. Patients exposed to certain factors suspected of being aetiological agents in dilated cardiomyopathy, such as excess consumption of alcohol and selenium deficiency, were included.

METHODS

Haemodynamic studies
Cardiac catheterisation was performed by the percutaneous technique through the femoral artery and vein. Right catheterisation was performed by means of a Swan-Ganz thermal dilution catheter which permitted measurement of pressure and cardiac output.

The left ventricle was catheterised with a pigtail catheter by the retrograde femoral approach. Cinefilms of left ventriculography were obtained in the 30° right anterior oblique projection after injection of 45 ml of Renografin. The ejection fraction was measured by means of digital callipers.

Selective cineangiography of the coronary arteries was performed by the Judkins’ technique; images were obtained in at least five planes for the left coronary artery and two for the right.

Left ventricular endomyocardial biopsy
Endomyocardial biopsy of the left ventricle was carried out by the long sheath technique. A specially designed 8.5 French Teflon catheter with a haemostatic valve and side arm (Ikram sheath, Cook Inc, Australia) was inserted into the femoral artery over an 8 French pigtail catheter and advanced into the left ventricle. Multiple biopsy specimens were taken by means of a King’s biotome and fixed in glutaraldehyde for electron microscopy and formaldehyde for light microscopy. Morphometric analysis of the biopsy specimens was carried out as described elsewhere.

Biochemical analyses
Concentrations of blood selenium were measured by the method of Watkinson. Plasma transketolase concentrations were measured by the method of Warnock.

Epidemiological methods
(a) Social class was defined according to occupational status; (b) alcohol excess was established by clinical assessment and by response to the Canterbury alcoholism screening test; (c) cigarette smoking was measured as pack years—that is, the number of packets of 20 cigarettes smoked per day multiplied by the number of years the subject had smoked; (d) survival was calculated from the first hospital admission for cardiac disease (follow up details were obtained by outpatient evaluation in surviving patients and from relatives, family doctors, and the Registry of Births and Deaths for those who had died); (e) sudden death was defined as death occurring within 24 hours without previous symptoms.

Statistical methods
Standard descriptive statistical variables such as the means, standard deviations, and standard errors were calculated by standard formulas and a BMDP program. The influence of selected clinical, haemodynamic, and biochemical variables on survival was examined by the life table method with program PII of the BMDP statistical package. The generalised Wilcoxon and the generalised Savage tests were used to evaluate the significance of a particular variable on survival. The Wilcoxon test is more sensitive to short term effects, whereas the Savage test is more suitable for long term trends.

Results

Only four patients were lost to follow up. They were counted as being alive up to their last follow up visit.

DEMOGRAPHIC FEATURES

Incidence
Since 1975 there have been 72 cases of dilated cardiomyopathy in a population of 350,000. This gives an annual incidence of 2.0/100 100 population. This is almost certainly an underestimate because some cases will have been referred to other physicians. The case incidence remained fairly constant at six per annum except for 1977 when there was a three-fold increase.

Age, sex, and race
The ages at time of catheterisation ranged from 22 to 74 years with a mean (SD) of 50.15 (10.64) years. Eighty one per cent of the patients were men and 86% were white; the remainder were Maori. The number of Maoris was disproportionately high because only 2% of the total referral population were Maoris.

Social and educational status
The majority of the study population were unskilled labourers but there were very few unemployed
Dilated cardiomyopathy

people (table 1). Executive, managerial, and professional classes were conspicuously absent and only one person had a university degree.

CLINICAL FEATURES

Presenting symptoms
The commonest presenting symptom at the first cardiac admission was dyspnoea. Table 2 shows the other major symptoms.

Physical examination
The commonest physical finding was cardiomegaly. Table 2 lists the frequency of other physical findings.

Electrocardiographic findings
Only 7% of patients presented with an entirely normal electrocardiogram. The most frequent findings were non-specific repolarisation changes.

Radiological findings
The cardiothoracic ratio was increased in all the patients at the time of catheterisation. The degree of cardiomegaly was the strongest predictor of both long and short term prognosis.

HAEMODYNAMIC DATA
Of the many haemodynamic variables that were assessed only the pulmonary arterial pressure correlated significantly with prognosis. The left ventricular ejection fraction was one notable index that did not predict survival.

MODE OF DEATH
Half of the patients died suddenly. In 67% death occurred out of hospital. Of those not dying suddenly, 67% died of progressive cardiac failure and two died of massive pulmonary emboli. Non-cardiac deaths were due to accident in two and suicide in one. The cause of death could not be established in six cases.

Table 1 Social and educational data on 72 patients with catheter diagnosed idiopathic dilated cardiomyopathy in New Zealand

<table>
<thead>
<tr>
<th>Social and educational status</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>White collar</td>
<td>2</td>
</tr>
<tr>
<td>Blue collar</td>
<td>22</td>
</tr>
<tr>
<td>Unskilled labourer</td>
<td>27</td>
</tr>
<tr>
<td>Housewife</td>
<td>9</td>
</tr>
<tr>
<td>Student</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>3</td>
</tr>
<tr>
<td>Retired</td>
<td>5</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2</td>
</tr>
<tr>
<td>Chronic sickness benefit</td>
<td>1</td>
</tr>
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</table>

Table 2 Symptoms and signs at presentation of 72 patients with idiopathic dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>61 (85)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>26 (36)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Fainting</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Embolic</td>
<td>4 (6)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Signs:</th>
<th></th>
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<tbody>
<tr>
<td>Clinical cardiomegaly</td>
<td>46 (64)</td>
</tr>
<tr>
<td>Ascites</td>
<td>36 (50)</td>
</tr>
<tr>
<td>Raised jugular venous pressure</td>
<td>37 (51)</td>
</tr>
<tr>
<td>Oedema</td>
<td>23 (32)</td>
</tr>
<tr>
<td>Third heart sound</td>
<td>23 (32)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Rales</td>
<td>17 (24)</td>
</tr>
</tbody>
</table>

SURVIVAL DATA

Figure 1 shows our results and the results of two studies from the United States 16,17 and one from Germany 18 that had similar inclusion criteria. The mean survival time for our series was 85 months. This is similar to that in two other studies. 16,18 The study of Fuster et al has a slope identical with that in the other two studies but a different intercept, suggesting that the patients had more advanced disease but that their attrition rate was similar to ours. 17 Table 3 lists the factors influencing survival.

Discussion

Though the term idiopathic dilated cardiomyopathy is a convenient description for a syndrome resulting from cardiac muscle dysfunction it does not describe a homogenous entity. Even this broad definition is a misnomer because the same cardiac dysfunction can occur in the absence of dilatation 19 or be confined to one ventricle. 20 With growth of knowledge and

Fig 1 Cumulative survival from first cardiac admission in the present series of dilated cardiomyopathy and in three others with similar entry criteria.
techniques, specific aetiological agents will be identified and reclassified as distinct disorders.

Our study shows that the incidence of dilated cardiomyopathy in New Zealand is similar to that in other developed countries.24 The various risk factors resemble those noted in other countries. The preponderance of men1 6 17 22 and those in the lower socioeconomic classes13 24 has been reported by others. Of other factors thought to be of aetiological importance, alcohol is the most commonly reported. Some authorities consider that alcoholic cardiomyopathy is a specific entity which should not be classified as idiopathic dilated cardiomyopathy. Alexander reported a series of 100 patients with cardiomyopathy, 83 of whom were judged to be alcoholics.25 His definition of excess alcohol consumption was at least four pints of beer or two measures of whisky a day. By these criteria 28% of his non-cardiomyopathic hospital admissions were alcoholics. Brigden and Robinson, on the other hand, defined alcoholism as a daily intake of 15 pints of beer or a 750 ml bottle of spirits.26 This variation illustrates some of the problems in attempting to define the role of alcohol in this disorder. Furthermore, unexceptional quantities of alcohol may be associated with cardiomyopathy in some individuals but not in others. Virtually all workers are agreed that it is exceptional to have evidence of other alcohol related disease in these patients. Diagnosis is complicated by the great difficulty in obtaining a reliable estimate of alcohol intake in alcoholics or even establishing whether the patient is drinking or not. Alcohol abuse also rarely occurs in isolation—it is often associated with cigarette smoking and faulty nutrition. Some series have reported improved survival in patients who became abstinent27; however, others have not.28 In our series about 50% of the patients were believed to be alcoholic, which is a lower percentage than some studies.26 27 The survival curves for alcoholics and non-alcoholics were identical, however (fig 2). This casts doubt on the primary aetiological role of alcohol.

The increased frequency of dilated cardiomyopathy in low socioeconomic classes, poorer countries, and in alcoholics has led to the suggestion that it may be related to faulty nutrition rather than a direct effect of alcohol. The nutritional factor most investigated has been thiamine. Cardiac beriberi is a distinct clinical entity and not readily confused with dilated cardiomyopathy. It was present in 20% of Alexander's cases25 and in 9-5% of our entire cardiomyopathic series. In the present study, however, we noted that a mildly abnormal transketolase test, which is not diagnostic of beriberi, was not rare and that it significantly predicted survival. Since this test indicates thiamine deficiency it suggests that subclinical deficiency of thiamine is frequent and does influence survival and may be aetiologically important. The validity of this observation can only be proved by a controlled trial of thiamine administration, but the present data are highly suggestive of such a relation.

Recent studies on animal models29 30 and patients31 suggest that smoking may have an aetiological role in dilated cardiomyopathy even in the absence of coronary vascular disease. About 35% of our series of patients were cigarette smokers; this is no more than in the general population. In the absence of a control group we cannot assess the aetiological importance of cigarette smoking. The survival data do show a worse prognosis with increasing cigarette smoking. The reasons for this remain speculative but they may relate to the increased risk of sudden death in smokers.32 Since half our patients died suddenly, smoking may be an important prognostic factor.

Selenium deficiency was first described as a cause of myopathy (including cardiomyopathy) in New Zealand lambs.33 34 Our referral population comes from an area which has one of the lowest soil selenium contents in the country. The human equivalent of this animal cardiomyopathy is Keshan dis-

Fig 2 Comparative cumulative survival from first cardiac admission for idiopathic cardiomyopathy (51 cases) and alcoholic cardiomyopathy (21 cases).
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ease, a dilated cardiomyopathy endemic to the Keshan region of China where the soil is very deficient in selenium. If selenium deficiency is an aetiological factor in dilated cardiomyopathy in New Zealand an incidence of epidemic proportions would be expected; this is not the case. In Keshan, however, the mean concentration of blood selenium in affected individuals was 20 µg/ml whereas unaffected residents had a mean concentration of about 40 µg/ml. (J Watkinson, 1985, personal communication.) The mean concentration in our cardiomyopathy patients was 57.8 µg/ml, which although it is lower than the concentration in healthy blood donors from our area (42 to 190 µg/ml) and the United States (100 to 340 µg/ml), is not as low as in Keshan patients. The reason for the lack of selenium related cardiomyopathy in New Zealand may simply be that the concentrations of the trace metal are not low enough to cause the disease in man, who may be less susceptible than animals. Alternatively, selenium deficiency may be only one of the factors responsible. Not all Chinese experts agree that selenium deficiency is the most important factor in the aetiology of Keshan cardiomyopathy. 

Without a controlled trial of selenium supplements we cannot be certain about the aetiological importance of selenium deficiency; however, we found that once the condition is clinically obvious the concentration of blood selenium had no bearing on prognosis.

Our data indicate that the prevalence of various proposed aetiological agents of idiopathic dilated cardiomyopathy is the same in New Zealand as elsewhere. This suggests that the cause or causes of this condition lie in common factors that are universally present.

The course of dilated cardiomyopathy in Australasia is largely unknown. This study suggests that the prognosis is relatively good. The mean survival of 85 months is significantly better than the study reported from the Mayo Clinic in which 75% of patients died within the first two years. It is also better than the survival of patients with coronary artery disease and a history of heart failure; these patients had a mean survival of four years irrespective of their New York Heart Association functional class. Franciosa et al also reported a better prognosis in dilated cardiomyopathy than in coronary disease. Reports from many countries report a long survival in patients with dilated cardiomyopathy. Kuhn from West Germany, Segal et al from the United States and Hatle from Norway, who all date their survival from the first definite cardiac symptoms, report a survival experience similar to ours. Even the series from the Mayo Clinic in which a very poor survival rate was reported shows an identical slope to our study and the other studies—only the intercept is different. This suggests that the attrition rate in all these series is the same; the different intercept indicates that the series with shorter survival had included patients with more advanced disease. A similar difference in prognosis between major teaching hospitals and district hospitals has been reported for hypertrophic cardiomyopathy.

Survival was unrelated to sex or to race. Increasing age was associated with a poorer prognosis. This observation was also made by others but denied by some. Cardiac size on the chest radiograph emerged as the best predictor of prognosis in this series as in several others. The adverse prognostic significance of atrial fibrillation was also confirmed. The predictive value of haemodynamic measurements was disappointing, particularly that of the left ventricular ejection fraction. This is a much debated point; some find it of great value while others do not. The same is true of myocardial histology. Like others we did not find that the results of myocardial biopsy added further prognostic information, but there are reports that histological changes are independent predictors of survival.

These patients die either of progressive cardiac failure or of sudden unexpected death presumably caused by an arrhythmia. There is disagreement about the proportions of deaths caused by these two mechanisms. Our findings were similar to those of Johnson and Palacios who reported a 45% frequency of sudden death in their series. Segal et al reported a 29% frequency of sudden death, but they also reported that an additional 10% of their deaths were caused by arrhythmias. Sudden death is undoubtedly common in these patients.

The course of the disease followed three patterns. The first was inexorable decline with death in one to two years. The second was deterioration followed by stabilisation and even temporary improvement in some, followed by further decline, the whole course being long drawn out (>15 years). We have, however, never seen complete recovery in a patient with established cardiomyopathy. The third pattern of natural progress is a variable, often slow, decline ending in sudden unexpected death. This latter course, which often occurs in patients with haemodynamically mild disease, may prevent a close relation between haemodynamic variables and prognosis.

It is difficult to judge the influence of treatment on survival in an uncontrolled study such as this. The only class of drugs that may improve prognosis in heart failure are the angiotensin converting enzyme inhibitors and even for these the evidence is slim. We compared the survival in our patients before
1980, when these drugs first became available to us, with survival after this time. We were unable to show any significant differences; however, the numbers were small.

This study shows that the clinical syndrome of dilated cardiomyopathy has virtually the same incidence, aetiology, and course in New Zealand residents as in other European populations. It suggests that some commonly encountered factor or factors are responsible for this disorder.

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