Cardiomyopathy in western Denmark

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SUMMARY A retrospective study was carried out to assess the incidence of cardiomyopathy in western Denmark (Jutland and Funen) (population 2 798 000) during a two year period (1980-81). The WHO/ISCF classification was strictly followed, and rigid criteria for exclusion and inclusion of patients were adopted. Thus cases in which specific heart muscle disorders (myocarditis, alcoholic heart disease, hypertension etc) were merely suspected were excluded. Forty one patients had dilated cardiomyopathy (overall incidence 7.3/10⁶ population/year) and 20 hypertrophic cardiomyopathy (overall incidence 3.6/10⁶ population/year). In men aged 40-59 years the occurrence of dilated cardiomyopathy was 23.4/10⁶ population/year. Only one case of Löffler's endomyocardial disease was diagnosed during the study period. Since the investigation was retrospective and was a study of diseased persons and not a population, and since a specific set of criteria for exclusion and inclusion was rigidly applied, the results represent the minimum frequency of these diseases.

When reviewing cardiomyopathies more than 10 years ago Oakley emphasised that there was "an apparent contentment with the diagnosis of coronary heart disease in our western society."¹ This attitude has changed, as evidenced by the vast number of published reports on cardiomyopathy and lately on myocarditis. Nevertheless, the fundamental question of the occurrence of cardiomyopathy as defined by the WHO/ISCF Task Force Group² is still largely unknown; only Torp's study³ from the Malmö area in southern Sweden offers an answer to that question.

We carried out a retrospective study in western Denmark (Jutland and Funen) to establish the frequency of cardiomyopathy in that region.

Patients and methods

The clinical notes or necropsy reports or both were retrospectively studied for all patients in western Denmark (Jutland and Funen, population 2 798 000) who had a first time diagnosis of cardiomyopathy (ICD code number 425) during the period 1 January

1980 to 31 December 1981. All the survivors were investigated at one of the three cardiac departments serving this demographically well defined area. Information on the necropsy results was obtained from the 12 departments of pathology and the two institutes of forensic medicine in the area.

EXCLUSION CRITERIA

Following the recommendations of the Task Force Group on cardiomyopathy² we adopted strict criteria for the exclusion and inclusion of patients. Those initially suspected of cardiomyopathy were excluded if they had: (a) a history of arterial hypertension or diastolic blood pressure >95 mm Hg (n=2) or both; (b) an estimated alcohol consumption >70 g/day for at least five years (n=2); (c) a history of (severe) acute infection during the three months before the onset of cardiac symptoms (n=2); (d) a history and electrocardiographic changes suggesting previous myocardial infarction (electrocardiographic changes of that type alone have prompted further investigation as it is known they may occur in some patients with normal coronary arteries suffering from cardiomyopathy^{4,5}) (n=2); (e) physical findings or haemodynamic examination or both suggesting primary valve disease (n=4); and (f) endocrine or metabolic disorders, neurological (heredofamilial) and systemic disorders, peripartum heart disease, and toxic reactions (n=4).

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INCLUSION CRITERIA

In addition to having symptoms and physical signs suggesting cardiomyopathy⁶ the patients included in the study fulfilled the following echocardiographic or angiographic criteria for inclusion:

Hypertrophic cardiomyopathy—echocardiographic criteria:⁷ (a) interventricular septal thickness ≥ 13 mm, (b) interventricular septal thickness to left ventricular posterior wall thickness ratio ≥ 1.5 , and (c) systolic anterior movement of the anterior mitral leaflet (at least two of three echocardiographic criteria had to be positive if the diagnosis was based on echocardiography alone); **angiographic criteria:**⁸ (a) elimination of the mid-portion and apex of the left ventricular cavity during systole or (b) pronounced systolic narrowing of the mid-portion of the left ventricular cavity.

Dilated cardiomyopathy—echocardiographic criteria: (a) left ventricular internal diameter in diastole (LVIDD) ≥ 57 mm⁹ (correction for body surface was carried out when necessary) and (b) reduced contractility of the left ventricle with left ventricular ejection fraction (EF) ≤ 0.45 ¹⁰ ($EF = (LVIDD^3 - LVIDS^3) / LVIDD^3$ where LVIDS is the left ventricular internal diameter in systole); **angiographic criteria:** (a) left ventricular end diastole volume > 100 ml/m²¹⁰ and; (b) reduced contractility with ejection fraction ≤ 0.45 .

Electrocardiography

Electrocardiographic findings were based on standard 12 lead recordings; only in a few cases was Holter monitoring performed as well.

Medication

Only five patients with dilated cardiomyopathy were taking systemic medications before the onset of cardiac symptoms. One woman was taking an oral contraceptive agent, one prednisolone because of bronchitis, one indomethacin because of arthralgia, and one a neuroleptic drug (thioridazine). One patient had previously been treated with a tricyclic antidepressant (amitriptyline).

Morphological criteria

The histopathological criteria for establishing a diagnosis of cardiomyopathy were strictly followed as described in several reports.^{11 12} Cases of suspected myocarditis (due to inflammatory cell infiltration in excess and cell degeneration or necrosis¹³) (n=1), coronary heart disease (defined as a luminal atherosclerotic reduction $> 50\%$ or infarction fibrosis) (n=2), and valve disease were excluded. Whatever the morphology cases of specific heart muscle disorders² (including patients with known hypertension in the past and excessive alcohol consumption) were excluded (n=4).

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Results

During a two year period (1980–81) a diagnosis of cardiomyopathy was established in 62 patients in Jutland and Funen. This gives an overall incidence of 7.3/10⁶ population/year of dilated cardiomyopathy (n=41) and of 3.6/10⁶ population/year of hypertrophic cardiomyopathy (n=20). Löffler's endomyocardial disease was found in only one patient.

FAMILY HISTORY

A family history of heart disease other than of ischaemic or valvar origin was present in 28% of patients (proved in 15%) with dilated cardiomyopathy and in 54% of patients (proved in 31%) with hypertrophic cardiomyopathy.

SEX AND AGE DISTRIBUTION

The age of patients with dilated cardiomyopathy ranged from 8–79 years and with hypertrophic cardiomyopathy from 19–84 years. Table 1 shows the sex and age distribution. Almost twice as many male as female patients had dilated cardiomyopathy, whereas the sex distribution was equal in those with hypertrophic cardiomyopathy. More than half of the male patients with dilated cardiomyopathy (n=14) were between 40–59 years old (population 299 000), which gives a frequency of 23.4/10⁶ population/year for dilated cardiomyopathy in this group.

DIAGNOSIS

A diagnosis of cardiomyopathy was initially based on cardiac catheterisation or echocardiographic investigation (Table 2). An 8 year old girl had dilatation of the

Table 1 Sex and age distribution in patients with cardiomyopathy

Age (yr)	Dilated cardiomyopathy		Hypertrophic cardiomyopathy	
	Male	Female	Male	Female
0–19	1	1	1	1
20–39	6	3	5	3
40–59	14	4	3	4
≥ 60	6	6	0	3
Total	27	14	9	11

Table 2 Diagnosis of cardiomyopathy and number of deaths

Diagnostic procedure	Dilated cardiomyopathy (n=41)	Hypertrophic cardiomyopathy (n=20)
Catheterisation	27	14
Echocardiography	23	12
Necropsy alone	11	4
Confirmed by:		
Necropsy	19	6
Surgical biopsy	0	3
Died (no necropsy)	2	0
Died (total number)	21	6

right ventricle only (right ventricular internal diameter in diastole 24 mm); the pressures in the right ventricle were normal and there were no arteriovenous shunts. An intraventricular pressure gradient (mean 68 (range 20–112) mm Hg) was found in 10 of 14 patients with hypertrophic cardiomyopathy in whom catheterisation was performed.

Coronary arteriography showed no abnormalities in 14 patients with dilated cardiomyopathy and in six with hypertrophic cardiomyopathy. In addition, necropsy showed normal coronary arteries in 17 patients with dilated cardiomyopathy and in five patients with hypertrophic cardiomyopathy. Thus normal coronary anatomy was found in 31 (76%) patients with dilated cardiomyopathy and in 11 (55%) with hypertrophic cardiomyopathy.

Necropsy alone established the diagnosis of dilated cardiomyopathy in 11 patients. Of these, seven had experienced symptoms (especially dyspnoea) for 1–9 years and were among the eldest patients (mean age 66 (range 41–79) years), whereas four died suddenly with no known symptoms of heart disease. During the study period and the following six months 10 patients with dilated cardiomyopathy died (mean age 45 (range 24–65) years). In eight of these necropsy was performed. The diagnosis of dilated cardiomyopathy was thus confirmed at necropsy in 19 (46%) patients.

In the group with hypertrophic cardiomyopathy surgical biopsy during myomectomy (three patients) or necropsy specimens (six patients) confirmed the diagnosis in nine (45%) patients. Two of the six patients in whom necropsy was performed had no known symptoms of heart disease. Altogether four patients with hypertrophic cardiomyopathy died suddenly.

SYMPTOMS

Patients with dilated cardiomyopathy had one or more symptoms for a mean period of three years (range 0–17 years) before the diagnosis was established, whereas those with hypertrophic cardiomyopathy had had symptom(s) for a mean of five years (range 0–22 years).

Dyspnoea was the most prevalent finding in both groups, although heart failure was almost exclusively found in patients with dilated cardiomyopathy (Table 3). One patient with dilated cardiomyopathy had systemic embolism. A systolic murmur was found in nearly all patients with hypertrophic cardiomyopathy compared with less than half of those with dilated cardiomyopathy (Table 3).

ELECTROCARDIOGRAPHIC AND RADIOLOGICAL DATA AND BLOOD PRESSURE

Table 4 shows the radiological and electrocardiographic data. An increased cardiothoracic ratio was

Table 3 Symptoms and signs at the time of diagnosis in patients with cardiomyopathy. Figures are numbers per total number of patients (%)

	Dilated cardiomyopathy	Hypertrophic cardiomyopathy
Left heart failure	26/37 (70)	1/18 (6)
Right heart failure	13/37 (35)	0/18 (0)
Systolic murmur	17/37 (46)	16/17 (94)
Dyspnoea	31/41 (76)	10/20 (50)
Chest pain	9/41 (22)	7/20 (35)
Palpitation	7/41 (17)	3/20 (15)
Syncope	3/41 (7)	2/20 (10)
Unexpected death	4/41 (10)	2/20 (10)
Symptoms in NYHA class:		
I	7/41 (17)	7/20 (35)
II	6/41 (15)	8/20 (40)
III	18/41 (44)	4/20 (20)
IV	10/41 (24)	1/20 (5)

Table 4 Radiological and electrocardiographic data in patients with cardiomyopathy. Figures are numbers per total no of patients (%)

	Dilated cardiomyopathy	Hypertrophic cardiomyopathy
Cardiothoracic ratio >0.5	31/35 (89)	9/17 (53)
Intermittent or chronic atrial flutter or fibrillation	12/37 (32)	4/18 (22)
Left bundle branch block	11/37 (30)	0/18 (0)
Left ventricular hypertrophy (ECG)	9/37 (24)	15/18 (83)
Right bundle branch block	1/37 (3)	1/18 (6)
Left anterior fascicular block	2/37 (5)	0/18 (0)
Inverted T waves	14/37 (38)	12/18 (67)
Complete atrioventricular block	2/37 (5)	0/18 (0)
Sinoatrial block	1/37 (3)	0/18 (0)

found in nearly all patients with dilated cardiomyopathy and in half of those with hypertrophic cardiomyopathy. Left ventricular bundle branch block was found exclusively in patients with dilated cardiomyopathy. Left ventricular hypertrophy was noted in 24% of patients with dilated cardiomyopathy and in 83% of those with hypertrophic cardiomyopathy. Chronic or intermittent atrial flutter or fibrillation was found in 32% of patients with dilated and in 22% of those with hypertrophic cardiomyopathy. Of the patients who died suddenly or had syncope one with dilated cardiomyopathy was in asystole on admission and two had ventricular fibrillation (one was resuscitated). In the hypertrophic cardiomyopathy group one was in asystole on admission and one had ventricular fibrillation, from which he died.

Systemic blood pressure did not differ between the two groups (mean (SD) systolic pressure 113 (16) and 121 (20) mm Hg; diastolic pressure 77 (11) and 72 (12) mm Hg in patients with dilated (n=37) or hypertrophic (n=16) cardiomyopathy respectively).

The only case of Löffler's endomyocardial disease in this series was in an early acute form in a 37 year

old woman who died of subarachnoid haemorrhage (ruptured, non-mycotic aneurysm of the right posterior cerebral artery). Histological sections of the heart showed numerous eosinophilic granulocytes and recent small areas of necrosis.

Discussion

During the two year period of the study the diagnosis of cardiomyopathy based on catheterisation or echocardiography or both could be established only at the three cardiac departments serving the region of western Denmark. We assumed that all patients with suspected cardiomyopathy were referred to one of these three departments, an assumption for which we have verbal confirmation. The necropsy data were collected from the 12 departments of pathology and two institutes of forensic medicine in the area, and all available specimens for histological examination were studied by the same pathologist.

Our criteria for inclusion and exclusion may not be universally acceptable. A review of the literature shows, however, that specific and detailed criteria are difficult to find or are non-existent. It was therefore necessary to formulate such criteria, which we consider are sufficiently precise for future comparison.

There are several reasons why our figures may appear low; they are certainly minimum figures. Firstly, we did not investigate a population but only assessed the available information in patients in whom cardiomyopathy was already diagnosed. Thus we are faced with all the problems of a retrospective survey: how often was a correct diagnosis of cardiomyopathy missed? were all the patients with cardiomyopathy referred?

Secondly, and most importantly, we made our criteria so rigid that a suspicion of any specific heart muscle disorder (for example) resulted in exclusion from the study. Dilated cardiomyopathy is thought to be a condition of multifactorial origin.¹⁴ In particular, (viral) myocarditis may be the cause of a proportion of cases probably by way of an immunological pathogenesis.¹⁵ The problem is, however, that there is a large grey zone of overlapping conditions: chronic myocarditis, healed myocarditis, sequelae of myocarditis, and dilated cardiomyopathy. It should be emphasised that our approach was to exclude patients in whom a diagnosis of present or past myocarditis was suspected. We made every possible effort to exclude coronary heart disease, which may mimic cardiomyopathy clinically (especially dilated cardiomyopathy).

The incidence of cardiomyopathy varies in different parts of the world; not only varying diagnostic criteria but also geographical differences affect the figures. Löffler's endomyocardial disease is certainly much

more frequent in Africa than in Europe.¹⁶ To our knowledge, Torp's study from Sweden³ is the only one of the incidence of dilated cardiomyopathy. Since there are probably no major differences between the population of southern Sweden and western Denmark his data should be comparable with ours. Nevertheless, Torp found the incidence of dilated cardiomyopathy to be seven times higher than we did. How can this be explained?

The study population of 250 000 in Torp's study was served by only one hospital. In our area many general departments of internal medicine were concerned in the study, and, although all three cardiac departments of the region participated in the investigation, some patients may have escaped referral to one of these during the study period. Torp reports a necropsy rate of about 90% for admitted patients; no figure is given for patients dying outside hospital. In our target area necropsy was performed in 30% of all deaths during the study period.¹⁷ Fifty four per cent of deaths occurred in hospital, and of those approximately 50% were examined at necropsy. These figures certainly point to an underestimation of the incidence.

In Torp's study the only specific criteria for a diagnosis of dilated cardiomyopathy were based on a mean pulmonary artery wedge pressure of >12 mm Hg at rest and of >16 mm Hg during submaximal exercise, a heart size >500 ml/m², and a cardiac index and stroke volume index <2.8 l/min/m² and <30 ml/beat/m² respectively. These criteria would include "early cases" or cases of suspected cardiomyopathy. In the present study, however, we aimed to include only definite cases of cardiomyopathy.

The mortality rate in Torp's study (nine out of 59 patients died over a period of eight years) was lower than that in ours (10 out of 41 patients died during a two and a half year period).

Thus the patients included in the two studies differ because of the varying strictness of the diagnostic criteria; furthermore, a study period of eight years including follow up of suspected cases would favour a higher frequency of the disease than a two year study without follow-up. Patients in whom minor signs or findings were inconclusive might have the diagnosis confirmed later on. In that case, however, the figures are not a one year incidence rate but merely a combination of the incidence and prevalence of the disease.

Impairment of systolic function does not produce heart failure unless the left ventricular ejection fraction is <0.4 .¹⁸ Since lesser degrees of systolic dysfunction is of limited clinical importance a left ventricular ejection fraction <0.4 has been proposed before a diagnosis of dilated cardiomyopathy is established.^{18 19} Our criteria of an ejection fraction of <0.45 and the fact that 70% of the patients had left heart failure support our use of this criterion. The

finding of four (10%) patients with no known cardiac symptoms in the group of patients with dilated cardiomyopathy further illustrates the difficulties of estimating the occurrence of the disease.

In our study the number of patients with hypertrophic cardiomyopathy was about half that of those with the dilated type. This figure includes patients with symptomatic disease and those who died without any known heart disease. This result is lower than previously suggested especially if asymptomatic cases are included.^{3 20} Specific data are, however, not available.

Our investigation indicated that relatives of about 50% of the patients had hypertrophic cardiomyopathy, although this was proved in only 31% of the patients. These relatives were identified previously because of their symptoms and did not influence our results. Since asymptomatic forms of hypertrophic cardiomyopathy may be detected by echocardiography the incidence of that disorder would undoubtedly be higher if this study had been undertaken as a screening procedure. A family history of dilated cardiomyopathy in 28% of patients with dilated cardiomyopathy and in 54% with hypertrophic cardiomyopathy compares well with the findings of Emanuel *et al.*'s study from 1972.²¹

The present data indicate the minimum figures for the occurrence of symptomatic cardiomyopathy confirmed at necropsy obtained by a retrospective survey in western Denmark. A prospective study would undoubtedly show a higher frequency. More precise data would, however, require a population study based on an echocardiographic evaluation with subsequent coronary arteriography and histological examination of biopsy specimens in cases suspected of dilated cardiomyopathy. A study of this design is not possible for practical and ethical reasons, and the many problems of defining early cases would still remain. A definition of disease including the terms unknown/idiopathic is not satisfactory but is unfortunately often realistic. Increased insight and experience in determining the incidence of such disorders will naturally reduce the number of cases; in the study of the cardiomyopathies great progress has been made during the past 20 years. Thus Löffler's endomyocardial disease could probably be omitted from the cardiomyopathy group and be transferred to the group of specific heart muscle disorders when the WHO/ISCF Task Force Group issues new guidelines.

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References

- 1 Oakley CM. Clinical definitions and classification of cardiomyopathies. *Postgrad Med J* 1972; 48: 703-13.
- 2 Report of the WHO/ISCF task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980; 44: 672-3.
- 3 Torp A. Incidence of congestive cardiomyopathy. *Postgrad Med J* 1978; 54: 435-7.
- 4 Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972; 34: 545-52.
- 5 Gau GT, Goodwin JF, Oakley CM, *et al.* Q-waves and coronary arteriography in cardiomyopathy. *Br Heart J* 1972; 34: 1034-41.
- 6 Goodwin JF. Myocardial diseases. *Medicine (Oxford)* 2nd ser. 1977; 25: 1286-96.
- 7 Doi YL, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M-mode echocardiography in hypertrophic cardiomyopathy: diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; 45: 6-14.
- 8 Goodwin JF. The frontiers of cardiomyopathy. *Br Heart J* 1982; 48: 1-18.
- 9 Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea & Febiger, 1981.
- 10 Vokonas PS, Gorlin R, Cohn PF, Herman MV, Sonnenblick EH. Dynamic geometry of the left ventricle in mitral regurgitation. *Circulation* 1973; 48: 786-96.
- 11 Roberts WC, Ferrans VJ. Pathological anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. *Hum Pathol* 1975; 6: 287-342.
- 12 Olsen EGJ, Baandrup U. Histopathological aspects of cardiomyopathy and the role of endomyocardial biopsies. In: Sekiguchi M, Olsen EGJ, eds. *Cardiomyopathy. Clinical, pathological and theoretical aspects*. Tokyo: University of Tokyo Press; Baltimore: University Park Press, 1980; 89-106.
- 13 Baandrup U, Olsen EGJ. Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy. I: Morphological and morphometric aspects. *Br Heart J* 1981; 45: 475-86.
- 14 Goodwin JF. Introduction, problems and aims of the multicentre research project. *Postgrad Med J* 1978; 54: 431-2.
- 15 Olsen EGJ. Myocarditis—a case of mistaken identity? *Br Heart J* 1983; 50: 303-11.
- 16 Brockington IF, Olsen EGJ. Löffler's endocarditis and Davies' endomyocardial fibrosis. *Am Heart J* 1973; 85: 308-22.
- 17 Causes of Death in Denmark 1980 and 1981. National Board of Health, Copenhagen, 1982 and 1983.
- 18 Johnson RA, Palacios I. Dilated cardiomyopathies of the adult (part I). *N Engl J Med* 1982; 307: 1051-8.
- 19 Feild BJ, Baxley WA, Russell RO Jr, *et al.* Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction. *Circulation* 1973; 47: 1022-31.
- 20 Shapiro LM, Zenzulka A. Hypertrophic cardiomyopathy: a common disease with a good prognosis. *Br Heart J* 1983; 50: 530-3.
- 21 Emanuel R, Withers R, O'Brien K. Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet* 1971; ii: 1065-7.