

The Causes of Dilated Cardiomyopathy: A Clinicopathologic Review of 673 Consecutive Patients

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Objectives. The purpose of this study was to document the various causes of dilated cardiomyopathy in a large group of adult patients with congestive heart failure.

Background. Previous reports of the causes of dilated cardiomyopathy have usually been case reports of a single specific etiology or review articles. The frequency of any single specific heart muscle disease is largely unknown.

Methods. We evaluated 673 patients referred for congestive heart failure due to dilated cardiomyopathy. The evaluation included medical history, physical examination, routine blood chemistry and hematologic measurements, electrocardiography and echocardiography. Thyroid function tests, antinuclear antibody tests and urinary vanillylmandelic acid and metanephrine levels were also obtained. Endomyocardial biopsy with right heart

catheterization was performed in every patient. Coronary arteriography was performed in patients who had at least two standard cardiovascular risk factors or a history suggestive of myocardial ischemia. The cases were retrospectively reviewed, and a final cause for dilated cardiomyopathy was listed for each patient.

Results. The most common causes of dilated cardiomyopathy were idiopathic origin (47%), idiopathic myocarditis (12%) and coronary artery disease (11%). The other identifiable causes of dilated cardiomyopathy made up 31% of the total cases.

Conclusions. Idiopathic dilated cardiomyopathy is a common cause of congestive heart failure. Specific heart muscle diseases occur with much less frequency.

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Cardiac dilation with left ventricular systolic dysfunction, which we have called dilated cardiomyopathy, is the most common cause of congestive heart failure (1). This disorder has many causes including idiopathic dilated cardiomyopathy, which we have defined as a primary heart muscle disease of unknown cause. The purpose of this study was to review the causes of dilated cardiomyopathy in a large unselected group of adult patients referred for the evaluation of congestive heart failure.

Methods

Subjects. Between December 29, 1982 and December 31, 1991, 673 patients were evaluated by The Johns Hopkins Hospital Cardiomyopathy Service for congestive heart failure due to dilated cardiomyopathy. The patients usually dated the onset of symptoms to within the previous 6 months. The majority (83%) of patients referred for evaluation had dilated cardiomyopathy, and all of these patients were included in this study.

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Protocol. The initial evaluation included a medical history, physical examination, routine blood chemistry and hematologic measurements, electrocardiography and echocardiography. The medical history included specific questions related to the cause of the cardiomyopathy, such as the amount of alcohol consumed per day. Thyroid function tests, antinuclear antibody titers and urinary vanillylmandelic acid and metanephrine levels were measured to evaluate specific heart muscle diseases. Coronary angiography was performed in patients with a history suggestive of myocardial ischemia or in the presence of at least two standard cardiovascular risk factors. These risk factors included age >35 years, hypertension, hypercholesterolemia, a positive family history of early coronary artery disease, diabetes mellitus, male gender and tobacco use.

Endomyocardial biopsy was performed in all 673 patients, preferably by way of the right internal jugular vein with the use of a Stanford-Caves biptome. At least four specimens were obtained from the right side of the ventricular septum. The tissue was immediately placed in either 10% formalin for light microscopy or 3% glutaraldehyde for electron microscopy. A separate sample was fresh-frozen for immunoperoxidase staining. Each specimen, stained with hematoxylin-eosin for light microscopy, was examined at a minimum of four levels by one investigator (G.M.H.). Special stains, such as Congo red for amyloid, were used when appropriate. Immunoperoxidase stains performed on the fresh-frozen tissue included stains for common leukocyte

Table 1. Characteristics of the 673 Study Patients

Men	423 (63)
Age (yr)	
Mean	45 ± 15
Range	9-85
No. ≤20 yr	19 (3)
No. ≥70 yr	24 (4)
Right atrial mean pressure (mm Hg)	7 ± 6
Mean wedge pressure (mm Hg)	17 ± 10
Cardiac output (liters/min)	4.5 ± 1.4
Cardiac index (liters/min per m ²)	2.3 ± 0.7
Blood pressure (mm Hg)	123 ± 24/78 ± 14
Heart rate (mm Hg)	91 ± 19

Unless otherwise indicated, values represented are mean value ± SD or number (%) of patients.

antigen and T-lymphocyte subsets, as well as class I and II antigen expression. Only the initial biopsy procedure was considered for analysis if the patient underwent a follow-up biopsy. After endomyocardial biopsy, 607 patients (90%) had right-sided cardiac catheterization performed with a fluid-filled, balloon-tipped, flow-directed catheter attached to a quartz transducer. Cardiac output was determined with the thermodilution technique performed in triplicate with <10% variability between determinations. Cardiac index was calculated in the usual manner.

Definitions. Standardized diagnostic criteria were used. The diagnostic categories were expanded from criteria developed by Coughlin et al. (2), utilizing the World Health Organization (WHO) Task Force recommendations on the Definition and Classification of Cardiomyopathies (3). The WHO Task Force did not include histologic examination of cardiac tissue as part of their classification. The definitions used in the present study are included in the Appendix.

Data analysis. A final diagnosis was recorded for each patient at completion of the evaluation. These diagnoses were retrospectively reviewed separately by two of us (E.K.K., K.L.B.) to ensure accuracy. Differences of opinion were settled through discussion. The results were prospectively computerized for tabulation. Results are expressed as mean value ± SEM.

Results

Patient characteristics (Table 1). A total of 673 consecutive patients were evaluated for congestive heart failure due to dilated cardiomyopathy. Their baseline characteristics are presented in Table 1. Most patients were adult men. Endomyocardial biopsy was performed by way of the right internal jugular vein in 656 patients (97%); an average of 6 ± 2 specimens/patient were obtained. Coronary arteriography was part of the evaluation in 220 patients (33%).

Final diagnoses (Table 2). The most common final diagnoses were idiopathic dilated cardiomyopathy, idiopathic myocarditis and coronary artery disease (ischemic cardiomyopathy). Myocarditis associated with a systemic disease

Table 2. Final Diagnoses

	Frequency	%
Idiopathic dilated cardiomyopathy	313	46.5
Idiopathic myocarditis	81	12.0
Coronary artery disease	74	11.0
Human immunodeficiency virus	33	4.9
Peripartum cardiomyopathy	33	4.9
Chronic alcohol abuse	23	3.4
Drug-induced cardiomyopathy (see text)	21	3.1
Connective tissue diseases (see text)	15	2.2
Amyloidosis	14	2.1
Hypertension	14	2.1
Familial cardiomyopathy	12	1.8
Metabolic (see text)	10	1.5
Valvular myopathy	10	1.5
Congenital heart disease	4	0.6
Neuromuscular diseases	4	0.6
Postcoronary bypass surgery	4	0.6
Sarcoidosis	4	0.6
Atrial fibrillation	1	0.1
Endomyocardial fibroelastosis	1	0.1
Histiocytosis X	1	0.1
Thrombotic thrombocytopenic purpura	1	0.1
Total	673	

such as systemic lupus erythematosus, human immunodeficiency virus (HIV) or peripartum cardiomyopathy was not included in the category of idiopathic myocarditis. There were 30 cases of borderline and 51 cases of active idiopathic myocarditis.

In the "drug-induced" category, cardiomyopathy was due to Adriamycin in nine patients, to cocaine in nine and to lithium, interleukin-2 and prednisone in one patient each (4). In the category of "connective tissue diseases," cardiomyopathy was due to progressive systemic sclerosis in seven patients, to systemic lupus erythematosus in five and to polyarteritis nodosa, polymyositis and rheumatic carditis in one patient each. Finally, in the metabolic category, cardiomyopathy was due to hyperthyroidism in four patients, to hypothyroidism in two, to hemochromatosis in three and to pheochromocytoma in one patient.

There were 115 specific diagnoses (17%) made on endomyocardial biopsy: myocarditis (n = 81), Adriamycin toxicity (n = 9), cardiac amyloidosis (n = 14), cardiac sarcoidosis (n = 4), cardiac hemochromatosis (n = 3), endomyocardial fibroelastosis (n = 1), histiocytosis X (n = 1), rheumatic carditis (n = 1) and thrombotic thrombocytopenic purpura (n = 1).

Discussion

This is the largest report of unselected adult patients with congestive heart failure due to dilated cardiomyopathy evaluated at a center with a specialized interest in cardiomyopathy. All patients underwent endomyocardial biopsy. An etiology for the dilated cardiomyopathy was found in 360

(53%) of the 673 patients; an idiopathic origin was diagnosed in the other 313 patients (47%). Most previous studies of the causes of dilated cardiomyopathy have been case reports concentrating on a single etiology. This study documents the frequencies of various causes of dilated cardiomyopathy in a large sample of adult patients with symptomatic congestive heart failure.

Several etiologies deserve special mention. Although the patients underwent an extensive search for specific causes of dilated cardiomyopathy, the condition was most commonly of idiopathic origin in this patient sample. Coronary artery disease was uncommon (11%), a finding that probably represents selection bias because patients with an ischemic cardiomyopathy might not have been referred for evaluation. In a primary care population, ischemic cardiomyopathy plays a much greater role (1). Similarly, the frequency of familial cardiomyopathy in this sample (1.8%) was smaller than previously reported (5), a difference that may have been due to our narrow definition of familial cardiomyopathy. A high incidence of biopsy-proved myocarditis was found in patients with both peripartum cardiomyopathy (74%) and HIV-related cardiomyopathy (56%). The relatively high frequency of both HIV-related cardiomyopathy and peripartum cardiomyopathy probably represents our interest in these disorders. Similarly, The Johns Hopkins Hospital serves an inner city population with a high prevalence of both cocaine and alcohol abuse. The single patient with dilated cardiomyopathy due to atrial fibrillation recovered normal cardiac function with conversion to normal sinus rhythm. His heart rate was not well controlled during atrial fibrillation.

Utility of endomyocardial biopsy. There is considerable controversy regarding the usefulness of endomyocardial biopsy. Monitoring for cardiac allograft rejection and anthracycline cardiotoxicity are the most widely accepted indications for endomyocardial biopsy (6). We were not able to address this question in the current study. The number of specific histologic diagnoses made on endomyocardial biopsy was 115 (17%). The utility of endomyocardial biopsy remains unclear.

Study limitations. Unlike previous studies, the present study used standardized clinical and pathologic diagnostic criteria. We tried to use criteria that were well established or at least agreed on by all of the authors. The existence of some categories, such as hypertensive cardiomyopathy and corticosteroid cardiomyopathy, are controversial. Similarly, arbitrary decisions were necessary in setting the defining characteristics of some categories.

Heart muscle disease may have multiple causes in any single patient with dilated cardiomyopathy. Although a single factor may predominate, this should not restrict the search for other potential causes that may exacerbate the condition. For example, a patient may have well developed ischemic cardiomyopathy worsened by a recent increase in alcohol consumption or the development of hypothyroidism.

All patients studied had been referred to The Johns Hopkins Hospital Cardiomyopathy Service for evaluation of

dilated cardiomyopathy. The Johns Hopkins Hospital is a tertiary care referral center that also serves a large primary care population. The majority (64%) of patients were referred to us by other cardiologists. These data are probably representative of other tertiary care institutions with a similar patient population. Selection bias limits the applicability of these data to primary care populations. Similarly, the patients studied had symptomatic congestive heart failure. The causes of dilated cardiomyopathy might be different in asymptomatic patients.

Appendix

Definitions

Idiopathic dilated cardiomyopathy. All patients with idiopathic dilated cardiomyopathy had a left ventricular diastolic diameter of ≥ 6 cm, with diffuse hypokinesia or akinesia and an ejection fraction $< 40\%$. They did not have clinical evidence of hypertensive, valvular, ischemic or congenital heart disease (7-11). A biopsy showing nonspecific changes, such as myocyte hypertrophy, nuclear abnormalities or interstitial fibrosis, was necessary for a diagnosis of idiopathic dilated cardiomyopathy (11). Patients with a normal biopsy result were excluded from this category because it was possible that they had a patchy process, such as myocardial sarcoid, that was missed because of sampling error.

Extramycocardial. Patients with *hypertensive* cardiomyopathy had a systolic blood pressure > 200 mm Hg or a history of poorly controlled hypertension of > 5 years' duration (12,13). *Ischemic* cardiomyopathy was defined by either a history of myocardial infarction or $> 50\%$ occlusion of one or more coronary arteries documented by coronary arteriography (14). Replacement fibrosis was often seen on endomyocardial biopsy. Patients with *valvular* cardiomyopathy due to mitral regurgitation had greater than grade 3/4 regurgitation, whereas patients with aortic regurgitation had greater than grade 2/4 regurgitation by angiographic analysis (15). The valvular regurgitation was known to have preceded the onset of cardiomyopathy. Patients with aortic stenosis had a calculated valve area < 1 cm² at cardiac catheterization (15). The presence of unrepaired congenital heart disease in the absence of other causes of dilated cardiomyopathy defined the cardiomyopathy of *congenital heart disease*. Cardiomyopathy associated with *coronary artery bypass surgery* was defined by new onset of cardiomyopathy after such surgery.

Myocarditis. Active or borderline myocarditis was a histologic diagnosis made according to the Dallas criteria (16); hence an endomyocardial biopsy was required. The diagnosis was confirmed by immunoperoxidase staining (> 10 common leukocyte antigen positive cells per high power field).

Metabolic. Cardiomyopathy due to *thyroid disease* occurred in patients with the appropriate abnormal thyroid function tests during the year before the onset of cardiomyopathy. Improvement of ventricular function with treatment of the thyroid disorder was required (17-22). *Pheochromocytoma* was diagnosed in patients with a history of pheochromocytoma documented by elevated urinary vanillylmandelic acid or metanephrine levels associated with an abnormal adrenal mass, or surgical removal of a pheochromocytoma or treatment with the appropriate alpha- and beta-receptor blocking agents (23,24). The diagnosis of *hemochromatosis* required

biopsy evidence of excessive myocardial iron deposits. A diagnosis of amyloidosis required the presence of myocardial amyloid deposits (25,26).

A diagnosis of collagen disease required clinical evidence of Marfan or Ehlers-Danlos syndrome. Connective tissue disease was diagnosed in patients with the appropriate clinical and laboratory studies. This category included systemic lupus erythematosus, polyarteritis nodosa, progressive systemic sclerosis, rheumatic cardiomyopathy and mixed connective tissue disorder (27-29). Sarcoidosis required pathologic evidence of myocardial noncaseating granuloma in an appropriate clinical setting (30,31).

Neuromuscular disorder was defined by the presence of a documented neuromuscular disease (32). Familial cardiomyopathy was diagnosed in the presence of clinical and anatomic evidence of cardiomyopathy in at least one first-degree relative (5,33,34).

Drug-induced cardiomyopathy. Anthracycline cardiomyopathy was diagnosed in patients with a history of receiving an anthracycline during the year before the onset of the cardiomyopathy associated with appropriate cardiac histologic findings (35-37). Heavy alcohol use, defined as the consumption of ≥ 8 oz/day of ethanol for ≥ 6 months or the treatment of alcoholism or alcohol withdrawal syndrome, was required for a diagnosis of a cardiomyopathy due to alcohol (38-43). Cocaine cardiomyopathy was defined by a history of cocaine use or positive findings on a drug screen (44-47). A history of receiving any drug known to cause cardiomyopathy (other than cocaine, ethanol or an anti-raclycline) before the onset of the cardiomyopathy associated with an eosinophilic myocarditis-defined drug-induced cardiomyopathy.

Peripartum cardiomyopathy. This was diagnosed if the onset of cardiomyopathy occurred during the last month of pregnancy or within 5 months after delivery (48). Human immunodeficiency virus (HIV)-induced cardiomyopathy was diagnosed in HIV-positive patients by enzyme-linked immunosorbent assay (ELISA) and Western blot analysis, without myocardial biopsy evidence of a specific myocardial infection (49-51). Neoplastic heart disease required biopsy or autopsy evidence of neoplasm, primary or metastatic, involving the myocardium (52). Likewise, endomyocardial fibroelastosis required histopathologic evidence. Arrhythmia required the recent onset of significant ventricular or supraventricular arrhythmias associated with myocardial dysfunction that lessened with treatment of the arrhythmia.

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