Assignment of Patients Into the Classification of Cardiomyopathies

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"... any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding ..."

(Goodwin JF: The frontiers of cardiomyopathy, Br Heart J 1982;48:1–18)

The conditions we now call cardiomyopathies were regarded as a diversity of "uncommon noncoronary myocardial diseases" in the 1950s. Goodwin and colleagues defined cardiomyopathies as "primary heart muscle diseases" and attempted their first classification in the 1960s. Subsequently, the definition and classification of cardiomyopathies were modified as their major structural and functional abnormalities were appreciated. Currently, cardiomyopathies are defined as "heart muscle diseases of unknown etiology." This definition distinguishes cardiomyopathies from other recognizable processes affecting the myocardium such as arterial hypertension and coronary, valvular, or congenital heart disease. The cardiomyopathies are also differentiated from "specific heart muscle disease" in which the myocardial disease is part of a known systemic disorder. This definition automatically excludes conditions in which the cause of the myocardial pathology or a specific pathological process can be clearly defined. However, this segregation is not accepted by all. Myocardial toxins such as alcohol and doxorubicin lead to ventricular dysfunction. Clinicians now often refer to alcoholic, adriamycin, or ischemic cardiomyopathy, so common use has eroded the distinction of the term "cardiomyopathy." Based on clinical, hemodynamic, and structural features, the WHO (World Health Organization)/ISFC Task Force classified the cardiomyopathies as dilated, hypertrophic, or restrictive. It was originally anticipated that some difficulties might arise in cases with overlapping features, such as hypertrophic and restrictive forms that have nondilated ventricles and abnormal diastolic function. As with any classification, it was thought that "a few cases that do not fit readily into any group" would remain unclassified. But the number of cases with unusual and overlapping features now representing "unclassifiable" cases is not trivial in our experience.

In recent years, our understanding of the cardiomyopathies has been affected drastically by the development and widespread use of noninvasive imaging techniques such as echocardiography and radionuclide angiography. These methods not only help us gain more information about sick patients but also allow us to recognize heart muscle disease early through screening of family members and other populations. As might be predicted, early detection of abnormal cardiac morphology, the ability to measure systolic and diastolic indexes of ventricular function, measurement of pressure gradients within the heart, and the ability to do repeated studies on individual patients have led to a broader interpretation of the cardiomyopathies. However, the wide spectrum of anatomic and hemodynamic findings definable with the newer noninvasive methods also is confounding to some degree. We now sometimes have difficulty in distinguishing cardiomyopathic abnormalities from physiological changes related to physical training, aging, or common conditions such as hypertension. Doppler echocardiography and nuclear angiography have revealed a striking heterogeneity of ventricular diastolic patterns, even among patients belonging to one disease category. Abnormal ventricular filling patterns may change even in the same patient, mainly because of complex but definable hemodynamic factors. Although the original classification of primary muscle diseases of the heart has withstood the test of time and is useful, the added information gleaned over the past several years has made the segregation of cardiomyopathies into discrete categories appear less clear now than it did when the classification was first suggested. The purpose of this discussion is to highlight some problems we have encountered in trying to organize our patients into the originally proposed classification in view of the subsequent literature.

Doppler Patterns of Ventricular Diastolic Filling

The characterization of diastolic filling by Doppler echocardiography has proven to be more complex than originally thought. The mitral inflow velocity signals accurately reflect pressure differences between the left atrium and left ventricle. However, multiple factors contribute to pressure and flow relations across the mitral valve. Abnormally slow left ventricle relaxation, with low left atrial pressure, gives rise to a pattern of slow acceleration of mitral flow in early diastole (E wave) with concomitant and probably compensatory increase in flow velocity with atrial contraction (A wave) (Figure 1). At the opposite end of the
spectrum are patients with stiff left ventricles giving rise to a very high early velocity (E wave) across the mitral valve with rapid equalization of atrial and ventricular pressures, which represents the dip-and-plateau pressure contour or square root sign, by catheterization. This pattern usually is accompanied by a diminutive A wave with atrial filling. Between these two ends of the spectrum is the normal filling pattern with the early filling velocity and flow–velocity integral somewhat larger than the atrial flow velocity and flow–velocity integral. However, we now recognize that these patterns are dynamic and highly dependent on both filling pressures within the heart and myocardial factors. 13,15,20,21 We hope to relate these patterns to the prior classification of the cardiomyopathies in the following discussion.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy is the least common type and the only cardiomyopathy without uniformly accepted diagnostic criteria. Its classic pathophysiological features include normal or near-normal ventricular size and contractility and a diastolic abnormality leading to rapid completion of filling in early diastole, with little or no further filling in mid or late diastole. 22–24 (Figure 2). This filling pattern, representing the cornerstone of the diagnosis, often corresponds to the dip-and-plateau contour of early diastolic pressure. The purest form of this category is the idiopathic restrictive cardiomyopathy, in which the classically defined hemodynamic abnormalities occur without specific histological changes. Restrictive hemodynamics have been described in many additional disease states that affect the heart. Of these, eosinophilic endomyocardial disease is included by the WHO/ISFC Task Force in its definition of restrictive cardiomyopathy, whereas other processes are considered systemic diseases that affect the heart. 25 It is not clear why amyloid confined to the heart, as opposed to systemic amyloidosis involving the heart, should be classified in a way different from that for eosinophilic endomyocardial disease. Amyloid probably is the leading cause of restrictive myocardial disease recognized clinically outside the tropics.

The diagnostic criteria of restrictive cardiomyopathy have been based on the extensively studied features of eosinophilic endomyocardial diseases and amyloidosis. Interstitial infiltration of the atria and ventricles lends the cardiac chambers a firm rubbery consistency in amyloidosis. 26 The diastolic filling abnormality in endomyocardial diseases appears to be related to the presence of a thick endocardial fibrotic shell with fingerlike penetrations into the myocardium. 27–29 This develops through a well-defined pathological process after initial damage induced by toxic eosinophils. 30–32 The fact that both an etiologic factor and a specific pathological process have been documented in endomyocardial diseases makes controversial their inclusion among primary cardiomyopathies. 33

Variability in the Restrictive Physiology of Eosinophilic Endomyocardial Diseases and Amyloidosis

Increased ventricular filling pressures with the dip-and-plateau pattern are the hemodynamic hallmarks of these diseases. Atrial pressures usually exceed 15 mm Hg, right atrial pressure is required to be more than 7 mm Hg, and pulmonary capillary wedge pressure is required to be more than 12 mm Hg. 22,30,31 In contrast with the equal left- and right-sided diastolic pressures in constrictive pericarditis, diastolic pressures are said to be separable by more than 5 mm Hg in restrictive myocardial disease due to unequal involvement and compliance of the two ventricles. 13,24,30,32 However, this separation usually is not seen at baseline in restrictive cardiomyopathy, and it often is not demonstrable despite provocative
tests such as volume loading, leg raising, exercise, or pharmaceutical interventions. Even the dip-and-plateau pattern may be absent in patients with restrictive myocardial disease. Patients with endomyocardial fibrosis or amyloidosis show ventricular filling abnormalities along a spectrum from the more advanced traditional restrictive type to the milder "abnormal relaxation" pattern (Figure 1). A recent Doppler echocardiographic study showed that early-phase amyloidosis is associated with abnormal relaxation. The restrictive type of filling was found only in advanced cardiac amyloidosis, with left ventricular wall thickness of ≥1.5 cm. Some patients with early amyloidosis had serial follow-up studies showing a change in filling from the abnormal relaxation pattern to the restrictive pattern, concomitant with progression of symptoms. The restrictive pattern indicated a poor prognosis. Thus, even in patients with endomyocardial fibrosis or amyloid heart disease, the paradigms of "restrictive myocardial disease," there is a range of diastolic abnormalities.

Previous Criteria for Idiopathic Restrictive Cardiomyopathy

The report of the WHO/ISFC Task Force actually does not include diagnostic criteria for this entity. A decade ago, Benotti and coworkers reported nine patients with heart failure, elevated right and left ventricular filling pressures, a dip-and-plateau diastolic pressure pattern, normal or near-normal systolic function, and absence of pericardial constriction or other known cause for these abnormalities. Several reports have been published using similarly strict hemodynamic criteria. In these reports, the diagnosis of idiopathic restrictive cardiomyopathy is supported by the absence of specific pathology on either endomyocardial biopsies or evaluation of whole heart specimens. In the accumulated series of 22 patients reported between 1980 and 1985, 95% were in New York Heart Association functional class III or IV, and their cardiac symptoms usually had been present for more than 5 years. The atria usually showed disproportionate dilation compared with the normal or near-normal ventricular size. The left ventricle showed notably normal or near-normal contractility and hypertrophy, usually of concentric type, in half of these 22 patients. Right ventricular hypertrophy (>0.5 cm) was found in eight (upper normal limit, 0.3 cm) and left ventricular hypertrophy (1.5 cm or more) was found in five of nine cases with pathological examination.

Histological evaluation was not distinctive and showed normal findings or nonspecific degenerative changes, including myocyte hypertrophy, mild to severe interstitial fibrosis, and the nuclear changes commonly found in all forms of cardiomyopathy. Mild myocardial fiber disarray was noted in only one patient. In one report, the microscopic and electron microscopic features of five explanted hearts with idiopathic restrictive cardiomyopathy were compared with findings in contemporary heart transplant recipients with dilated cardiomyopathy. Endocardial and interstitial fibrosis, degree of myocyte hypertrophy, and nuclear changes were similar in the two groups, but myofibrillar loss was absent in the restrictive cases and moderate or severe in those with dilated cardiomyopathy. Thus, histology did not explain the "stiff heart syndrome" of idiopathic restrictive cardiomyopathy.
Using less-stringent hemodynamic criteria, Hirota et al. reported 26 patients with heart failure as a result of idiopathic "stiff left ventricle," normal left ventricular systolic function, and absence of left ventricular hypertrophy (<1.3-cm wall thickness). This study included patients in functional class II, III, or IV and showed a 35% cardiac mortality rate over a mean follow-up period of 12 years. Although clinical and pathological findings were generally similar to those of previous cases of idiopathic restrictive cardiomyopathy, some differences bear special comment. Patients with left ventricular wall thickness of ≥1.3 cm were excluded from this study. A dip-and-plateau pattern was present in only 28% of cases in the left ventricle and in 50% of cases in the right ventricle. About one third of the patients had normal ventricular filling pressures. A family history of hypertrophic cardiomyopathy was found in five patients. Myocardial fiber disarray was found in 50% of patients, but it was severe in only 15%. Whether these four patients with severe disarray represented restrictive cardiomyopathy with disarray or an unusual subtype of hypertrophic cardiomyopathy without macroscopic hypertrophy, as described by McKenna et al., is not clear. The dip-and-plateau pattern was present in only half of the 10 patients with idiopathic restrictive cardiomyopathy in another recent report. This series included four patients with restrictive cardiomyopathy and heart block, two of whom had skeletal myopathy.

Suggested Criteria for Diagnosis of Idiopathic Restrictive Cardiomyopathy

Review of diagnostic criteria in both older and recent series shows general consensus for the diagnosis of restrictive cardiomyopathy in patients with clinical signs of heart failure in the presence of a nondilated, nonhypertrophic left ventricle with preserved contractility but abnormal diastolic function. The left ventricular ejection fraction ranged from 55% to 40% in five patients with end-stage disease requiring heart transplantation. Lack of consensus exists concerning two major diagnostic features: the type of diastolic filling abnormality required and the degree of ventricular hypertrophy allowed. We believe the dip-and-plateau pattern should not be considered an absolute requirement for the diagnosis of idiopathic restrictive cardiomyopathy. However, abnormal diastolic filling pressures on catheterization or filling pattern abnormalities (relaxation or restrictive type) on Doppler echocardiography or nuclear angiographic studies are essential for the diagnosis. Aggressive diuretic therapy may normalize the filling pressures and filling pattern. In the presence of unexplained signs and symptoms of heart failure with normal ventricular size and contractility, volume loading or pharmacological interventions should be used to attempt to unmask diastolic filling abnormalities.

Previous pathology studies have shown left ventricular wall thickness of ≥1.5 cm in 55% of patients with severe idiopathic restrictive cardiomyopathy and without myocardial disarray. We believe it is the restrictive hemodynamic pattern with signs and symptoms of heart failure that establishes the diagnosis of idiopathic restrictive cardiomyopathy in patients with mild-to-moderate degrees of hypertrophy. The absence of a left ventricular outflow tract gradient and negative family history for hypertrophic cardiomyopathy further support the diagnosis of idiopathic restrictive cardiomyopathy in patients with mild-to-moderate hypertrophy (Figure 3). Myocardial disarray, if present at pathology, should be quantified for proper assignment of patients with ventricular hypertrophy (see below). As a rule, idiopathic restrictive cardiomyopathy should be considered a sporadic disease, although occasionally it may show a familial occurrence with autosomal dominant transmission.

Distinction From Diseases Other Than Hypertrophic Cardiomyopathy

Restrictive cardiomyopathy presents a clinical and hemodynamic picture that frequently is indistinguishable from that of constrictive pericarditis. Because this latter entity is curable, all efforts should be made to establish the correct diagnosis. Endomyocardial biopsy is useful in revealing the presence of myocardial disease. In addition to echocardiography, there is an increased use of computed tomography and nuclear magnetic resonance to quantify pericardial thickness. Recent observations suggest that Doppler echocardiography is highly sensitive in distinguishing between advanced forms of constriction and restriction. Respiratory variations in left ventricular isovolumic relaxation time and peak early mitral and tricuspid flow velocity, as well as hepatic venous signals, were found in constrictive pericarditis but not in restrictive cardiomyopathy. The differentiation of idiopathic from secondary types of restrictive cardiomyopathy also is important in view of their different prognoses and therapies. Characteristics of 99mTc-pyrophosphate scan findings or echocardiography showing sparkling myocardial appearance are aids in detecting amyloidosis, but both lack high specificity and sensitivity. Idiopathic restrictive cardiomyopathy usually is not difficult to distinguish from secondary myocardial diseases with ventricular diastolic dysfunction such as diabetes mellitus or coronary disease. It is important to avoid overdiagnosis of idiopathic restrictive cardiomyopathy. Hypertension may lead to diastolic filling abnormalities, even without detectable left ventricular hypertrophy. There is a tendency for progressive development of the left ventricular relaxation abnormality pattern with age. This is so uniform that we may consider it a physiological phenomenon of aging. It is the development of heart failure that makes us believe a significant restrictive myocardial process also is present in some cases. The restrictive pattern of filling by Doppler echocardiography, which is associated with the dip-and-plateau pressure tracing, is pathological at any age, we believe.

Hypertrophic Cardiomyopathy

Early criteria for this condition emphasized asymmetric septal hypertrophy, outflow tract obstruction or gradient, and/or abnormal motion of the mitral valve as the diagnostic features of the disease. In subsequent years, it has become clear that no single feature is pathognomonic for idiopathic hypertrophic cardiomyopathy. The disease is genetically transmitted as an autosomal dominant trait with variable penetrance but with a high proportion of sporadic nonfamilial cases. The major common denominator of its diverse presentations is the idiopathic ventricular hy-
FIGURE 3. Heart specimens removed at transplantation, fixed in physiological shape, and photographed at equal scales. Panel A: Nondilated, nonhypertrophic heart that had hemodynamics typical of idiopathic restrictive cardiomyopathy. Panel B: Nondilated but hypertrophic heart that did not have myocardial fiber disarray but had hemodynamics typical of restrictive cardiomyopathy. (The authors also consider this case restrictive cardiomyopathy.) Panel C: Nondilated hypertrophic heart that had severe myocardial fiber disarray and a diastolic relaxation abnormality by Doppler echocardiography. This is considered typical hypertrophic cardiomyopathy. LV, left ventricle; MV, mitral valve; RV, right ventricle; TV, tricuspid valve. (Courtesy of Dr. Margaret E. Billingham, Stanford, Calif.)

Hypertrophy usually, but not always, associated with microscopic evidence of myocardial fiber disarray. Additional pathophysiological features include lack of ventricular dilation, normal or supernormal contractility, diastolic function abnormalities, disturbed intramural coronary morphology and flow, and an abnormal peripheral response to exercise. Although increased myocardial stiffness and abnormal relaxation coexist in hypertrophic cardiomyopathy, the dominant feature is impairment of the ventricular relaxation process. This usually results in a decrease in early diastolic flow velocity and volume and a compensatory
ventricular outflow gradient, may not be part of a cardiomyopathic picture. This feature also occurs in elderly patients with or without hypertrophy as a part of development of a "sigmoid septum." The relative contribution of hypertension and primary muscle disease is unclear in such patients.

Morphological and Histopathological Variabilities

The hypertrophy can involve the left ventricle, right ventricle, or both ventricles; can be a symmetric or concentric; and can be diffuse or localized to the proximal or distal septum, apex, or lateral or posterior wall. Recently, Klues et al. analyzed 94 mitral valves removed at necropsy or during surgery in patients with hypertrophic cardiomyopathy. They found that about 60% were abnormal in one or more aspects. This confirms the prior view that hypertrophic cardiomyopathy is a primary disease that involves not only the myocardium but also the mitral valve apparatus.

There is no histological feature that distinguishes hypertrophic cardiomyopathy from secondary hypertrophy. Myocardial disarray showed 93% specificity and 89% sensitivity for hypertrophic cardiomyopathy but only when found in more than 5% of the tissue analyzed. The disarray usually is located in the middle third of the septal myocardium and thus usually is missed by biopsy. Even if found on biopsy, it is not a pathognomonic finding as its extent cannot be appreciated from the small and haphazardly cut biopsy tissue. Fiber disarray also may occur in normal hearts or diseased hearts of other etiologies. The question of whether myocardial disarray should prevail over macroscopic hypertrophy as a marker of hypertrophic cardiomyopathy has been raised by a recent report of two families with a high incidence of sudden death, absence of macroscopic ventricular hypertrophy, but severe myocardial disarray on necropsy. Hirota et al. included this type of patient with restrictive cardiomyopathies, whereas McKenna et al. considered the entity "hypertrophic cardiomyopathy without hypertrophy." This unusual set of patients highlights the relative mutability of the gross morphological criteria previously thought to represent the cornerstone of diagnosis in hypertrophic cardiomyopathy.

Hypertrophic cardiomyopathy is a disease with remarkable variability of clinical, morphological, and pathophysiological presentations. A gene responsible for hypertrophic cardiomyopathy was recently located on chromosome 14 band 21. This finding opens the possibility of gene identification for definition and subtyping of patients now lumped together under the entity of hypertrophic cardiomyopathy. We may be able to observe clinically and morphologically silent carriers and understand the molecular and chemical etiologies for differences among forms of the disease. Hopefully, this approach will improve our ability to distinguish patients with hypertrophic cardiomyopathy from cases of physiological hypertrophy, older patients with morphological features of hypertrophic cardiomyopathy, and patients with restrictive cardiomyopathy who also have ventricular wall thickening. We need to better understand the variety of morphological presentations of hypertrophic cardiomyopathy among members of the same family. The genetic approach may improve definition of clinically silent carriers of the disease as

increase in late diastolic atrial contribution, i.e., the pattern we call a relaxation abnormality (Figure 1). But, again, the diastolic filling pattern may be altered by ventricular filling pressures, among other factors, and may appear normal. The intense study of these patients has led to an appreciation of the broad spectrum encountered regarding age, morphological and hemodynamic presentations, and natural history of the disease. This diversity has led to a growing tendency toward subtyping of patients with presumed implications for therapy and prognosis. It may also lead to inclusion of patients who do not belong in this category.

Age

Hypertrophic cardiomyopathy was initially recognized as a disease of youth and middle age, with absent or incomplete morphological presentation until late childhood or adolescence. After the age of 21 years, further progression of the hypertrophy is reportedly unusual. Hypertrophic cardiomyopathy is increasingly recognized in the aged with features similar to those found in young patients. Hypertrophy tends to be more frequently of the concentric type and is associated with hypertension in about half of the cases; the condition has a relatively good prognosis. One study found survival to be similar to that in an age-matched general population. Lever et al. reported that elderly patients with hypertrophic cardiomyopathy have a predominantly ovoid left ventricular cavity contour associated with a bulge of the basal septum in half of the cases. The septal bulge, which may induce or augment the left
well as the small but important minority of patients with a “malignant” course.86

Dilated Cardiomyopathy

Dilated cardiomyopathy generally is considered a multifactorial syndrome and a final result of many conditions that may insult the ventricular myocardium.4 Its major feature is dilation of the ventricles, which usually antedates the signs of heart failure. Patients with dilated cardiomyopathy characteristically have a globular poorly contracting left ventricle, whereas the right ventricular size and contractility may range from normal to severely abnormal. Mitral regurgitation that is mild to moderate is frequently found. Ventricular hypotrichotility, in the face of mitral regurgitation, points to primary myocardial disease. These patients may have both third and fourth heart sounds.

Diagnostic Difficulties

Usually, no difficulty is encountered in distinguishing patients with dilated cardiomyopathy from those in the two other classes of cardiomyopathy. Problems may arise in distinguishing dilated cardiomyopathy from other known processes that lead to a similar clinical and morphological presentation. Noninvasive methods sometimes are of limited value in distinguishing patients with dilated cardiomyopathy from those with advanced ischemic disease. The history and ECG often are not helpful. Reduced wall motion typically is diffuse in dilated cardiomyopathy and is more segmental in ischemic disease, but segmental wall motion abnormalities do occur in patients with dilated cardiomyopathy.87,88 The presence of a ventricular aneurysm is the only abnormality that significantly increases the odds of an ischemic etiology.87,88 Roberts and Ferrans4 showed extensive myocardial scarring in necropsy specimens of patients with dilated cardiomyopathy, and thallium perfusion scanning often is abnormal in cardiomyopathy patients.88 Positron emission tomography showed sensitivity of 100%, specificity of 80%, and diagnostic accuracy of 85% in distinguishing between primary myopathy and ischemic disease using tracers of both blood flow and glucose metabolism in patients with heart failure evaluated for heart transplantation.89 Separation of dilated cardiomyopathy from ischemic heart disease usually is attempted by coronary arteriography. In the presence of normal coronary arteries or disease of only minor branches, the diagnosis of dilated cardiomyopathy usually is reached. At the opposite extreme are cases of obvious multivessel coronary disease with previous infarction and with “ischemic myopathy.” However, we commonly encounter cases with significant stenosis of one or more major coronary vessels but no proven infarction and diffusely abnormal wall motion. That is, areas of the dilated poorly contracting ventricle are supplied by apparently normal coronary vessels. However, the angiographic demonstration of significant atheromatous disease in symptomatic patients probably implicates all vessels in the process.90 The classification of such cases is difficult, and we have not found a simple solution to this problem. Each case is assessed on the available details. The presence and importance of disease of the intramural coronary vessels have not been established.

In selected patients, endomyocardial biopsy is indicated to exclude myocarditis, granulomatous, and infiltrative diseases. Following standardization of the histopathological diagnosis of myocarditis by the Dallas criteria,91 evidence of myocarditis in dilated cardiomyopathy has been reported as 18–55%.92–95 The therapeutic implications of this finding are limited currently as the mere presence of inflammatory infiltrates does not necessarily signify active myocarditis.92 The possible link between viral infection and dilated cardiomyopathy, by either persistence of infection or autoimmune, has not yet affected the routine clinical management of these patients. Steroid therapy has proven to be of no benefit when routinely administered to patients with dilated cardiomyopathy in two randomized studies.94,95 However, endomyocardial biopsy may carry prognostic information in dilated cardiomyopathy. Figulla et al96 and Hammond et al93 found that no or only mild myofibrillar loss on biopsy was associated with either improvement or better survival during follow-up. This finding has not been confirmed in all subsets of dilated cardiomyopathy (see below). Biopsies also can be used for detection of metabolic defects.

Unusual Forms of Dilated Cardiomyopathy

The true etiology of dilated cardiomyopathy remains obscure in most cases. Nevertheless, associations with a wide variety of conditions have been documented and summarized by Kopecky and Gersh.97 Peripartum cardiomyopathy presents during the last trimester of pregnancy or during the first 6 months postpartum. Historical evidence of myocarditis was reported to be higher in such patients than in control populations.98,99 Spontaneous remission has been frequently documented, but mortality may be as high as 50%.98 It is not clear whether hemodynamic and other stresses associated with pregnancy “unmask a previously present cardiomyopathic diathesis” or, alternately, pregnancy confers a special sensitivity to cardiotoxic viruses.97 Mildly dilated congestive cardiomyopathy has been described as an unusual variant of dilated cardiomyopathy with distinctive features, whereas right ventricular cardiomyopathy probably represents a separate entity with some features resembling dilated cardiomyopathy.

We described mildly dilated congestive cardiomyopathy in patients with 1) end-stage heart failure of unknown etiology, 2) no or only mild left ventricular dilation, and 3) left ventricular ejection fraction of <30% in the absence of restrictive hemodynamics at catheterization.44 Compared with data of contemporary patients with idiopathic restrictive and dilated cardiomyopathy who also had heart transplantation, patients with mildly dilated congestive cardiomyopathy had an approximately 50% incidence of a family history of dilated cardiomyopathy, and their ventricular size was intermediate between restrictive and typical dilated cardiomyopathy. All other clinical, echocardiographic, hemodynamic, macroscopic, and light microscopic features were identical to those of dilated cardiomyopathy.45 Electron microscopy revealed moderate-to-severe myofibrillar loss in dilated cardiomyopathy and no or only mild myofibrillar loss in mildly dilated cardiomyopathy. The lack of cardiomegaly in mildly dilated congestive cardiomyopathy may be related to preservation of myofibrillar integrity.44,45 The diagnostic criteria of
mildly dilated congestive cardiomyopathy were prospectively applied in 12 patients followed without the availability of heart transplantation. Within 6 months of presentation, two patients developed significant cardiomegaly and died, and two additional patients improved or normalized their ejection fraction. The eight remaining patients with persistence of diagnostic criteria were followed for a mean of 18 months, and six of them died despite absence of significant cardiomegaly. The survival of these patients was significantly shorter than that of the transplanted patients.

Right Ventricular and Other Arrhythmogenic Cardiomyopathies

Clinical and pathological abnormalities of the left heart usually predominate in dilated cardiomyopathy. Rarely, abnormalities predominate on the right side. The association of sudden death and right ventricular disease in young individuals has stimulated a search for right ventricular cardiomyopathy, also called arrhythmogenic right ventricular dysplasia, no or only mild pathology is detected in the left ventricle. The right ventricular myocardial free wall is replaced by fatty, fibrous, or fibrolipomatous tissue. This entity of unknown etiology shows male predominance and usually is manifested at a young age with ventricular or supraventricular arrhythmias and sudden death. The ECG typically shows T wave inversion in leads V1 through V4, incomplete or complete right bundle branch block, variable QRS axis, and ventricular premature beats with the pattern of left bundle branch block and right-axis deviation. The pathological changes may be diffuse or may focally involve right ventricular outflow, inflow, or apical areas. On echocardiography and angiography, segmental asynergy is frequently found, but localized bulges, diverticular outpouchings, and deep fissuring of the ventricular contour are more specific indicators of the disease.

The incidence and natural course of right ventricular cardiomyopathy are not clear because most published series either are retrospective necropsy studies or include cases with severe arrhythmias referred to specialized centers. Initial reports of familial occurrence of the disease have been confirmed recently in nine families showing autosomal dominant transmission with variable expression and penetrance. Progression of echocardiographic and electrophysiological abnormalities have been documented during follow-up, leading to the concept of progressive replacement of the myocardium by fibrolipomatous tissue. This may represent the end result of an unusual healing process in which genetically susceptible individuals recover from a variety of unknown insults by deposition of adipose tissue. These fatty scars may then be the focus for the life-threatening arrhythmias classically associated with the disease. The presence of normal or near-normal thickness of the lipomatous or fibrotic myocardium distinguishes this disease from Uhl's anomaly. The latter is a congenital defect with absence of right ventricular myocardium from birth, usually associated with right heart failure in infancy, not with arrhythmias.

Right ventricular dysplasia has been characterized as an arrhythmogenic cardiomyopathy. In our opinion, the category of "arrhythmogenic cardiomyopathy" should include many additional patients currently considered to have idiopathic arrhythmias, as suggested by Sekiguchi et al. The basis of the arrhythmia often is obscure in otherwise young healthy individuals with grossly normal hearts and no evidence of mitral valve prolapse, ventricular preexcitation, or long QT interval. The origin of these arrhythmias probably is the result of pathological processes within the myocardium related to impulse generation and conduction. However, many of those having endomyocardial biopsy show abnormal myocardial histology.

This category may include patients with idiopathic life-threatening ventricular arrhythmias, some with lone atrial fibrillation, and many with persistent unexplained tachycardia. We have been impressed by the prevalence of a restrictive left ventricular filling pattern by Doppler echocardiography in patients with idiopathic atrial fibrillation (personal observation).

Conclusions

In a 1988 review, Goodwin noted that despite difficulties in assignment of some entities, such as mildly dilated congestive cardiomyopathy, right ventricular dysplasia, and certain conduction defects, the classification of cardiomyopathies into dilated, hypertrophic, and restrictive types has withstood the test of time. We agree with this statement in general but find that the categories do not have sharply defined edges and that the additional information now available to the clinician presents new problems in definition. There is hope for an improved, new classification based on an understanding of the genetics of some of these conditions. In the meantime, we have the practical problem of dealing with, for example, athletic patients with hypertrophic hearts and arrhythmias, elderly patients with abnormal relaxation patterns and clinical signs of congestive heart failure but excellent systolic function, and patients presenting with elements attributable to both dilated cardiomyopathy and coronary artery disease.

A great many conditions are now recognized in which a typical restrictive filling pattern of the left ventricle is seen. The majority of these have identifiable pathologies associated with them. Idiopathic restrictive cardiomyopathy is a rare condition, but we believe it should not exclude patients with ventricular hypertrophy. We have not seen patients with extensive ventricular hypertrophy of the degree that suggests typical hypertrophic cardiomyopathy in whom a typical restrictive filling pattern also was found (Figure 1). On this basis, we believe the presence of almost any degree of left ventricular hypertrophy is consistent with the diagnosis of restrictive cardiomyopathy when typical hemodynamics are present. To avoid compounding the diagnostic problems, we propose accepting patients into the category of restrictive cardiomyopathy in the presence of hypertrophy only with the typical pattern of restrictive physiology but not accepting them in what may be an early stage representing a relaxation abnormality (Figure 1).

We have encountered a large number of patients, predominantly those awaiting cardiac transplantation, with typical dilated cardiomyopathy who have a classic restrictive filling pattern by Doppler echocardiography or hemodynamic studies. We believe the predominant feature in these cases is the dilated heart with extremely poor contractility, so we consider them to represent dilated cardiomyopathy. Although these patients may
have reached the elastic limit of their myocardium or pericardium with resultant diastolic filling abnormalities similar to those seen in idiopathic restrictive cardiomyopathy, they are interesting but so far not confusing. We encounter difficulties placing a patient in the category of dilated cardiomyopathy if we find associated coronary disease or if extreme heart failure occurs without significant ventricular dilation. Advances in evaluation of immunologic markers of infection and autoimmunity may segregate postmyocarditis cases from idiopathic dilated cardiomyopathy.

Today, hypertrophic cardiomyopathy includes a wide spectrum of presentations, and we do not know if all of these variants belong to the same entity. The recent breakthrough in the genetics of some families may bring clarification regarding the unity of this class of myopathy. However, until such genetic testing and interpretation are widely available, problems remain in categorizing the commonly encountered athletic patients with ventricular hypertrophy and the elderly patients with hypertension who show features of hypertrophic cardiomyopathy. We chose to deal with these by focusing on features of the classification. If patients have a positive family history of hypertrophic cardiomyopathy or extensive myocardial fiber disarray on biopsy, this pushes us in the direction of classifying the individual patient within the spectrum of hypertrophic cardiomyopathy. If these are absent, we cannot exclude the diagnosis, but at least we have reduced the number of patients in whom the classification is ambiguous. The elderly patient with a sigmoid septum and no systolic anterior motion of the mitral valve or intraventricular gradient usually is not considered in this classification. In older patients with outflow gradients and more typical morphology for hypertrophic cardiomyopathy, we use a relatively empiric approach to treatment because of the literature on the therapy of this condition.

Right ventricular dysplasia probably should belong to a separate category of arrhythmogenic cardiomyopathies. This category also might include cases of life-threatening ventricular arrhythmias as well as some idiopathic atrial arrhythmias in the presence of myopathic changes on histological examination. In addition, we have noted a number of patients with long atrial fibrillation and a truly restrictive filling pattern by Doppler echocardiography. Such patients deserve further study and may represent a definable clinical entity.

The present state of knowledge does not justify a basic change in the classification of the cardiomyopathies, but perhaps the classification needs to be extended somewhat (see Table 1). Because more variants and subtypes are described using only morphological and hemodynamic features, one or more of the classic characteristics usually will aid assignment of the patient into a specific category as noted above. The Doppler patterns are most helpful in individual cases when combined with other aspects of patient data. We consider the classification to be like a tree having a few major branches that then subdivide into a complex and intricate crown. However, we do not know what accounts for the differences between the sometimes wild offspring and the original branch. Hopefully, the cellular and molecular genetic bases of these differences will be revealed in the near future and serve as the basis of a new classification.

Table 1. Primary cardiomyopathies

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<thead>
<tr>
<th>Condition</th>
<th>Dilated HCM Restrictive ARV</th>
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<tbody>
<tr>
<td>LV cavity enlargement</td>
<td>+</td>
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<td>Increased LV wall thickness</td>
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<td>Increased LV mass</td>
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<td>Decreased LV ejection fraction</td>
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<td>LV relaxation abnormality</td>
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<td>Restrictive LV filling pattern</td>
<td>+/−</td>
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<tr>
<td>Normalized Doppler LV filling pattern</td>
<td>+/−</td>
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LV, left ventricular; HCM, hypertrophic; ARV, arrhythmogenic and right ventricular; +, must be present; −, must be absent; +/−, may be present or absent; −*, left ventricle is rarely involved in right ventricular cardiomyopathy; +/−**, may be absent without provocative maneuvers.

The variation in Doppler diastolic patterns depends on the stage of the process and the loading conditions of the left ventricle. They are helpful when combined with the clinical, morphological, and systolic function parameters of the patient evaluated.

Summary

The original classifications of the cardiomyopathies based on anatomic criteria from radiographic and necropsy studies, as well as hemodynamic criteria from clinical and catheterization data, have been supplemented in recent years by information from noninvasive techniques. Echocardiography, radionuclide methods, and ambulatory ECG, in particular, have facilitated the ethical screening of family members and those less symptomatic than patients on whom the original classification was based. These powerful methods show a broad spectrum of anatomy and ventricular physiology along the natural history of and within the traditional categories of the cardiomyopathies. They also provide data on the effect of ventricular loading conditions affecting a range of diastolic filling patterns. This review has attempted to point out the areas of overlap among and/or controversy about the categories that have led us to a feeling of frustration when trying to neatly classify individual patients. The addition of filling patterns from Doppler echocardiography and nuclear angiography to the standard methods has been reviewed and hopefully will lend more perspective to the range of physiology seen in these conditions. The categories of cardiomyopathy should not be seen as excluding patients with the newly recognized variations in anatomy and ventricular filling patterns. Rather, the classification provides a framework on which to build and expand our understanding of these important conditions.

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Assignment of patients into the classification of cardiomyopathies.
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