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Pathology of Cardiomyopathies in Man (13-Nov-2004)

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Definition and Classification

The cardiomyopathies are a diverse group of myocardial diseases that are characterized by chronic ventricular dysfunction. The clinical classification of cardiomyopathy is based on hemodynamic and echocardiographic abnormalities, and consists of dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy. Recently, arrhythmogenic right ventricular dysplasia has been added to this classification [1] (Table 1). Hypertrophic and right ventricular cardiomyopathies have fairly distinctive morphological manifestations. Dilated and restrictive cardiomyopathies, on the other hand, are a more heterogeneous group of disorders without uniform histologic features. For this reason, the modifier "idiopathic" often precedes restrictive and dilated cardiomyopathy to emphasize that a variety of specific cardiac and systemic illnesses that may mimic these conditions has been ruled out. Secondary cardiomyopathies are termed "specific cardiomyopathies" in the recent World Health Organization classification [1] , and are primary diseases or the valves or coronary arteries, or are systemic illnesses with cardiac manifestations.

Table 1. Classification of cardiomyopathies [1]

- Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Arrhythmogenic right ventricular dysplasia
- Restrictive Cardiomyopathy
  - Idiopathic
  - Secondary
    - Amyloidosis[2]
    - Loeffler's eosinophilic endocardial fibrosis[2]
    - Tropical endocardial fibrosis (Davies disease)
- Unclassified cardiomyopathies
  - Mitochondrial cardiomyopathy
  - Fibroelastosis
  - Noncompacted myocardium
  - Systolic dysfunction with minimal dilatation[3]

Table 1. Classification of cardiomyopathies [1]

- Specific (secondary) cardiomyopathies
  - Ischemic cardiomyopathy
  - Valvular cardiomyopathy
  - Hypertensive cardiomyopathy
  - Inflammatory cardiomyopathy
    - Myocarditis
    - Chagas cardiomyopathy
    - HIV cardiomyopathy
  - Metabolic cardiomyopathy
  - General system disease
    - Connective tissue disease
    - Sarcoidosis
    - Leukemic infiltrates
  - Muscular dystrophies
  - Neuromuscular disorders
  - Sensitivity and toxic reactions
    - Alcoholic cardiomyopathy[4]
    - Anthracycline cardiomyopathy
    - Catecholamine cardiomyopathy
  - Peripartal cardiomyopathy[4]

[1]Adapted from Reference 1
[2]These conditions may also result in dilated ventricles, but are classically considered restrictive cardiomyopathies
[3]Related to minimally dilated cardiomyopathy, see text
[4]Occasionally considered in the spectrum of idiopathic dilated cardiomyopathy (see text)

Pathologists have historically used the term "cardiomyopathy" only for primary cardiac disorders, although clinicians often use the term (generally with modifiers) for secondary conditions (e.g., "ischemic cardiomyopathy") [2]. Only after clinical and pathologic exclusion of secondary causes of myocardial dysfunction (such as pericardial, hypertensive, congenital, valvular and ischemic disease) is the term "cardiomyopathy" strictly appropriate. However, the distinction between primary and secondary cardiomyopathy is sometimes arbitrary; for example, restrictive cardiomyopathy with endocardial fibrosis has been alternately classified as secondary or primary [1,2].

Dilated Cardiomyopathy
Definitions and Terms -
Dilated cardiomyopathy is an idiopathic disease of heart muscle that is characterized by impaired systolic function of both ventricles [3]. Clinically, approximately 50% of patients with congestive heart failure of unknown etiology will have no specific underlying cause demonstrated after complete evaluation, including endomyocardial biopsy [4]. In the other 50%, clinical investigation will reveal myocarditis and occult coronary artery disease in the majority; a host of other inciting agents (e.g. toxic insults secondary to anthracyclines or catecholamines) and systemic diseases (e.g. renal disease, hemochromatosis or amyloidosis) may also result in congestive heart failure. Pathologically, dilated cardiomyopathy is a term that should be restricted to cases of idiopathic global cardiac dilatation in the absence of significant coronary, valvular, and hypertensive disease, and other causes of cardiac dilatation such as cor pulmonale and congenital heart disease. In patients with conditions that are associated with dilated cardiomyopathy, such as chronic alcoholism, diabetes mellitus, and the peripartum state, the term is still often employed.

The use of "dilated cardiomyopathy" persists in the cardiology literature even for cases of cardiac dilatation secondary to coronary artery disease and other conditions [4,5]. To avoid confusion, the modifier "idiopathic" is often applied by clinicians to emphasize the absence of underlying diseases. In this chapter, however, "dilated cardiomyopathy" is synonymous with "idiopathic dilated cardiomyopathy".

Epidemiologic Features
The prevalence of dilated cardiomyopathy in the United States is about 37/100,000 individuals with a yearly incidence rate of 6/100,000. The mean age at presentation is in the fifth decade, typically between 20 and 60 years. Men are two to three times more likely than females to develop the disease. There is also a predilection for blacks.

Pathologic Features
Gross Pathologic Features - Cardiomegaly is morphologically considered a requisite for the diagnosis of dilated cardiomyopathy [6]. In some patients with dilated cardiomyopathy there is very little cardiac enlargement, however, and the diagnosis must be made largely on clinical grounds [7]. The mean heart weight in a large series of dilated cardiomyopathy was 615 grams (range 360 - 940 grams). Hearts weighing more than 700 grams are unusual, representing less than 3% of all cases in three compiled autopsy studies.

Typically, there is four-chamber dilatation (Table 2) which is greater in the ventricles than the atria. In patients with a history of atrial fibrillation, atrial dilatation may be prominent. At autopsy, left ventricular dilatation is best assessed by measuring the chamber cavity at the level of the papillary muscles in a transverse cut; any measurement > 4 cm (excluding the papillary muscles) is indicative of left ventricular dilatation. Concomitant right ventricular dilatation results in the typical globular appearance of the heart.
The increase in heart weight in patients with dilated cardiomyopathy is by necessity secondary to cardiac hypertrophy. However, left ventricular wall thickness may be normal, because of the ventricular dilatation.
The mitral valve annulus has been described as relatively normal in circumference. Mitral insufficiency may result from papillary muscle dysfunction secondary to ventricular dilatation and changes in ventricular wall shape. In contrast, tricuspid regurgitation results from annular dilatation.
Right-sided mural thrombi are present in approximately one-third of hearts, and left sided thrombi in nearly one-half. Endocardial fibrous plaques in the ventricles are less common, occurring in about 10% of cases. Endocardial plaques are believed to be the result of organized thrombi. Mild diffuse or patchy endocardial fibrosis, especially toward the ventricular outflow tracts, is frequent and is likely a result of cardiac dilatation.
The myocardium in dilated cardiomyopathy is generally grossly unremarkable. However, gross scars (excluding fibrosis of the papillary muscles), usually subendocardial, may be present in up to 23% of hearts. Transmural scars have also been reported.
The coronary arteries in dilated cardiomyopathy by definition should be less than 75% narrowed in cross-sectional area (severe coronary disease). However, it is not rare in autopsy practice to encounter hearts with the gross features of cardiac dilatation with severe coronary disease involving one vessel, in the absence of myocardial infarcts, hypertensive or valvular disease [8]. In such cases, it is difficult to explain cardiac failure on the basis of coronary occlusion. Because of the high prevalence of severe one vessel disease in Western populations, one would expect the coexistence of dilated cardiomyopathy and coronary artery disease. Patients with cardiac failure and limited (e.g., one-vessel) severe atherosclerosis have been diagnosed as ischemic cardiomyopathy [1].

Table 2. Autopsy pathologic features, dilated cardiomyopathy

Feature	**Frequency** [1]
Gross	
Cardiomegaly	95%
Ventricular dilatation	95% - 100%
Mural thrombi	50%
Mural plaques	10%
Subendocardial scars	10%
Transmural scars	2%
Histologic	
Myofiber hypertrophy	95%
Lymphocytic infiltrates	50% [2]
Subendocardial fibrosis	45%
Interstitial fibrosis, diffuse	15%
Myocarditis (Dallas criteria)	<5%

[1] These are approximate and may vary by definitions used
[2] > 5 foci in several histologic sections

Microscopic Features - The histologic features of dilated cardiomyopathy are non-specific (Table 2) [1] and may be seen in failing hearts of any cause. The classic histologic triad consists of myocyte hypertrophy, myocyte atrophy, and interstitial fibrosis [9]. However, the degree of fibrosis is quite variable [10]. Although myocyte hypertrophy is present in the vast majority of cases, the histologic appearance in some cases is essentially normal, supporting the concept that the primary defect is at a subcellular metabolic level.

Myocyte Changes - The myocyte hypertrophy characteristic of dilated cardiomyopathy is accompanied by increased nuclear DNA content and normal or reduced myocyte width due to myocyte attenuation [10]. The mean myocardial cell diameter in patients with dilated cardiomyopathy has been calculated at 22 microns, compared to 17 microns in control subjects [11]. It is typical to see a marked variation in myofiber size, especially when viewed on cross section. The myofibrillar loss results in the loss of contractile filaments and vacuolization of myocytes which may be related to decrease in ventricular contractility [10]. Several investigators have noted an association between percentage area occupied by myofibers (as determined morphometrically on endomyocardial biopsy) and cardiac ejection fraction. This association suggests that the degree of myofiber loss may have prognostic significance.

Inflammation - The degree of lymphocytic infiltrate has been a matter of debate. In autopsy hearts, Rose and Beck demonstrated no increase in lymphocytes compared to a control population, and clusters of lymphocytes are found in over 40% of trauma control hearts, as well as hearts with dilated cardiomyopathy. Tazelaar and Billingham found no infiltrates in 13%, 1 - 5 foci of at least 5 inflammatory cells in 33%, 6 - 30 foci in 47%, and 30 or more foci in 8% in generously sampled hearts from patients dying with dilated cardiomyopathy [12]. Areas of true myocarditis with adjacent myocyte necrosis are seen in fewer than 5% of cases. In endomyocardial biopsies from patients with recently diagnosed dilated cardiomyopathy, 13% demonstrate myocarditis by the Dallas criteria. The degree of lymphocytic infiltrate varies greatly by stage of disease, methods of sampling, and methods of lymphocyte quantitation.

Fibrosis - The type of fibrosis present in dilated cardiomyopathy is typically described as interstitial, although both interstitial and replacement fibrosis (with dropout of myocytes) have been described. The frequency of patchy interstitial and focal replacement fibrosis is approximately 15% and 45%, respectively. The types and extent of fibrosis found in cases of dilated cardiomyopathy was found to be similar to that found in hearts from patients dying of other cardiovascular and neoplastic diseases. The degree of fibrosis (as determined morphometrically) increases from the epicardium to the endocardium, and is greater on the left side of the ventricular septum than the right [11]. The endocardial predilection is secondary to subendocardial ischemic damage that is frequently seen in failing hearts.

The fibrosis of dilated cardiomyopathy is associated with a selective increase in collagen type I, which imparts stiffness and may accentuate diastolic dysfunction, and which may be mediated through upregulation of transforming growth factor (TGF) beta.

Small Vessel and Atrial Disease - The precapillary arterioles have been described as thickened in endomyocardial biopsies from patients with dilated cardiomyopathy. By computed morphometric analysis, the degree of atrial fibrosis is increased in patients with dilated cardiomyopathy compared to other forms of congestive heart failure, suggesting an intrinsic atrial defect that reflects the left atrial dysfunction that may be detected hemodynamically.

Ultrastructural Features - Ultrastructural changes of dilated cardiomyopathy consist primarily of interstitial fibrosis (increased numbers of mature and developing collagen fibrils in interstitial spaces), cellular hypertrophy (increased transverse diameters of muscle cells, increased size of nuclei and Golgi complex, and increase in mitochondria, glycogen, and ribosomes), and degenerative changes (cellular edema, increased lipid droplets, lysosomes and lipofuschin, and T-tubular dilatation) [6,9]. The most striking change is rarefaction or even complete loss of contractile elements [13]. Morphometrically, there is a mean increase in nuclear area, irregularity of the nuclear outline, and a decrease in mitochondrial area compared to controls [14].

The degree of myofibrillar loss appears to be increased in patients with marked cardiac dilatation, compared to those with minimal cardiac dilatation (mildly congestive cardiomyopathy).

Mitochondrial Disease - It has been reported that approximately 10% of patients with idiopathic dilated cardiomyopathy who undergo preoperative evaluation for heart transplantation demonstrate mitochondrial abnormalities in endomyocardial biopsy specimens [15]. These ultrastructural abnormalities include giant organelles, angulated, tubular, and concentric cristae, and

crystalloid or osmiophilic inclusion bodies. In these patients, nearly one-fourth demonstrate heteroplasmic mitochondrial DNA mutations that are associated with decreased levels of cytochrome c oxidase activity. It has been suggested that elevations of trace elements, especially mercury and antimony, may be the cause of mitochondrial abnormalities in some patients with dilated cardiomyopathy [16]. The significance of mitochondrial gene mutations in infantile and adult dilated cardiomyopathy is unclear.

Pregnancy - In approximately 25% of peripartum patients with heart failure, the etiology is idiopathic leading to the diagnosis of peripartal (dilated) cardiomyopathy [17]. Peripartum cardiomyopathy is defined as left ventricular dilation and failure, first developing during the third trimester of pregnancy or in the first 6 months postpartum. The pathologic features are similar to dilated cardiomyopathy in patients who do not meet these criteria. The incidence is approximately 10 in 100,000 births and the mortality is between 25 and 60%. Risk factors for peripartum cardiomyopathy include advanced maternal age, multiparity, African descent, twinning, and long-term tocolysis. The disease is occasionally familial.

In general, the incidence of myocarditis in peripartal cardiomyopathy is very low, similar to that of non-peripartal dilated cardiomyopathy. However, two studies have shown a high proportion (29 - 79%) of myocarditis at endomyocardial biopsy of patients with peripartal congestive heart failure. The varied frequency of inflammatory infiltrates may be partly due to terminology; peripartum myocarditis is occasionally classified separately from peripartum cardiomyopathy. /p>

Although the clinical features of peripartum cardiomyopathy do not differ from those of dilated cardiomyopathy (other than earlier age at onset and shorter duration of symptoms), it is often considered as an entity separate from dilated cardiomyopathy. The precise classification of this entity has not been resolved [1].

Hypertrophic Cardiomyopathy

Definition and Terms -

Hypertrophic cardiomyopathy is idiopathic ventricular hypertrophy in the absence of ventricular dilatation. It is a diastolic disorder that is characterized by restriction of ventricular filling. The clinical diagnosis rests on echocardiographic criteria, which include a nondilated hypertrophied left ventricle, with normal or increased ejection fraction [18]. The area of hypertrophy is often greatest at the base of the ventricular septum, resulting in asymmetric hypertrophy in a large proportion of patients. Left ventricular outflow obstruction occurs in a subset of patients, in whom the diagnosis of idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy is occasionally rendered. Currently, the term hypertrophic cardiomyopathy is preferred for all morphologic variants of the disease, however.

Clinical and Epidemiologic Features

Epidemiologic Features - The prevalence and yearly incidence of hypertrophic cardiomyopathy in Olmsted County, Minnesota, have been estimated at about 20/100,000 and 2.5/100,000, respectively. Echocardiographic abnormalities suggestive of the disease are found in a much higher proportion of the population, with a prevalence of 170 - 500/100,000 in the United States [19]. The disease may occur at any age, although most patients are in their 30's or 40's at the time of diagnosis. In a recent clinical series of 600 patients, the mean age was 45 (range 7 - 79 years), and 66% of patients were men. Males were affected one and one-half times as frequently as females in one multicenter study. Currently, with implementation of screening regimens for relatives of patients with known disease, hypertrophic cardiomyopathy is being diagnosed frequently in adolescents and children.

Pathologic Features

Gross Pathologic Features (Table 3) - *Heart Weight* - The heart is typically enlarged to approximately twice normal weight. The mean heart weight in a series of 40 autopsied cases was 634 grams 6 and weights of over 1,000 grams may be encountered [6,20]. However, the heart weight may be minimally enlarged or even normal, especially in cases of apical hypertrophic cardiomyopathy. In sudden death, the heart may appear grossly normal and the diagnosis made only on the basis of histologic criteria. Recently, cardiac hypertrophy has been shown to be a predictor of sudden death in patients with hypertrophic cardiomyopathy.

Site of Hypertrophy - The cardiac hypertrophy is secondary to ventricular thickening, usually asymmetrical, that may occur almost anywhere in the ventricular mass, but most often in the ventricular septum. Maron et al have classified hypertrophic cardiomyopathy into four morphologic groups. Type I signifies asymmetric hypertrophy involving only the anterior segment of the ventricular septum (usually at the base). Type II is defined by diffuse thickening of the septum without free wall involvement. Type III denotes thickening of the ventricular septum and the anterior free wall. Finally, type IV involves

thickening involving any parts of the ventricle other than the anterior basal septum, including the posterior septum, the anterolateral free wall, or the apical portion of the left ventricle. Asymmetric hypertrophy (the maximal septal thickness significantly thicker than the ventricular free wall) is present in up to 90% of cases. The minimum ratio of septal thickness to free wall thickness that signifies asymmetry is subjective and arbitrary, but is generally at least 1.3:1 pathologically and 1.5:1 by echocardiography. Portions of the right ventricle may be involved both grossly and histologically. The most common site of involvement in the right ventricle is the posterior wall, often towards the apex.

The gross features of apical hypertrophic cardiomyopathy differ from other types. The heart weight may be only mildly increased, and the apex of the ventricular septum demonstrates scarring and myofiber disarray which may be grossly visible and involve the right ventricle and left ventricular septum.

Evolution of Gross Features - In early stages of disease, the left ventricular cavity is small, and there is usually left atrial dilatation resulting from decreased left ventricular compliance. In children, there may be relatively rapid accumulation of myocardial mass, with 250% increases in ventricular thickness occurring over 3 - 6 years. In later stages of disease, there may be gradual dilatation of the left ventricle, and areas of hypertrophy may be partly replaced by grossly discernible fibrous tissue. The replacement of hypertrophied areas by scarring may transform previously hypertrophied areas of ventricular wall to normal or even thin ones, and transmural scars may be present in the absence of epicardial coronary occlusions. Occasionally, there may be diffuse gross myocardial scarring in late stages of disease. The evolution of morphologic features must be considered if autopsy findings are compared to cardiac imaging performed years prior to death.

Endocardial and Valvular Pathology - A left ventricular outflow tract plaque is present in up to 73% of hearts [6]. In contrast to congenital subaortic stenosis, the area of endocardial fibrosis is limited to that opposite the anterior leaflet of the mitral valve. The frequency of a left ventricular outflow tract plaque is 95% in patients with documented subaortic stenosis by catheterization, and less than 50% in patients without subaortic stenosis [6]. The area of stenosis may be surgically removed to relieve outflow tract obstruction. Currently, percutaneous ethanol injection into the ventricular septum is performed in lieu of surgical correction.

The anterior leaflet of the mitral valve is typically thickened in cases of outflow tract obstruction, and there is often a mismatch in the lengths of the anterior and posterior leaflets, resulting in systolic anterior motion of the anterior leaflet. In a study of 94 valves from patients with mostly the obstructive form of hypertrophic cardiomyopathy, the mean anterior leaflet length was greater than that of a control group of mitral valves, and increased mitral leaflet area was found in 58%. In addition, nine patients had a congenital malformation of the mitral apparatus in which one or both papillary muscles inserted directly into anterior mitral leaflet. The abnormal insertion of the papillary muscle onto the left ventricular outflow tract is an important variant to recognize before surgical myomectomy is attempted. The abnormalities of the mitral valve may predispose to infectious endocarditis. Endocarditis occurs in approximately 4 per thousand patients, with higher rates in patients with left atrial dilatation and left ventricular outflow tract obstruction.

Table 3. Autopsy pathologic features, hypertrophic cardiomyopathy

Feature	Frequency [1]
Gross	
Cardiomegaly	95%
Asymmetric hypertrophy	90%
Subendocardial scars	80%
Left ventricular outflow tract plaque	60%
Mitral valve prolapse	3%
Transmural scars	2%
Apical septal hypertrophy	1% [2]
Histologic	
Myofiber disarray >5% of VS	85%
Intramural coronary artery thickening	83%
Interstitial fibrosis	95%

[1] These are approximate and may vary by definitions used and phase of illness
[2] Up to 25% in the Japanese

Microscopic Pathologic Features (Table 3) - *Myofiber Disarray* - The most characteristic microscopic feature of hypertrophic cardiomyopathy is myofiber disarray (also called myocyte disarray, myocardial disarray [22], and myocyte disorganization [23]. Unlike hypertrophy secondary to increased volume or pressure load, hypertrophic cardiomyopathy results in a very uneven increase in myocyte size reflected by myocyte disorganization at a subcellular level. The histologic manifestations of myocyte disarray include oblique alignment of myocytes, producing a whorled, tangled, or pinwheel configuration. In addition, the shape of myocytes is abnormal, with branching fibers common, and lateral attachments are increased. The degree of myofiber disarray is variable, but averages 30% of the septal myocardium and is usually greater than 5% [23,24].

The proper histologic evaluation of myofiber disarray is dependent on taking cross-sections of the ventricular septum, to avoid artifacts of tangential or longitudinal sections.

The sensitivity and specificity of the histologic diagnosis of myofiber disarray (compared to hearts from normal controls and hearts with other cardiac diseases resulting in cardiac hypertrophy) is approximately 86% and 90%, respectively. These high sensitivity and specificity figures result when a cut-off point of 5% of septal cross sectional areas is used for the designation of myofiber disarray [23,24]. For pathologic practice, we section 5 - 6 areas of ventricular septum in cases of suspected hypertrophic cardiomyopathy: 3 from the basal septum (anterior, mid-septum, and posterior), and 2 - 3 from the apical septum. Because sections of ventricular septum are typically large, it is occasionally necessary to divide the section of septum into two pieces. However, the need for cross sections cannot be overemphasized in the proper evaluation of myofiber disarray. In many cases of hypertrophic cardiomyopathy, myofiber disarray is also present in the ventricular free wall, corresponding to the gross subtypes described by Maron et al. [18].

Conditions that may result in myofiber disarray other than hypertrophic cardiomyopathy include other causes of ventricular hypertrophy, including aortic stenosis and chronic hypertension. However, the degree of myofiber disarray in these conditions is generally minimal, and less than 5%. Normal hearts may demonstrate myofiber disarray at the junction of the free walls and septum. The myocyte disarray of hypertrophic cardiomyopathy is characterized by a greater enlargement of myocyte size in the affected region (usually in the middle third of the ventricular septum) than in the subendocardial areas in the same section of myocardium. Myofiber disarray is usually accompanied by increase in fibroblasts and collagen, the former predominating in early stages, and the latter in later stages of disease.

Abnormal patterns of desmin immunoreactivity have been described in areas of myofiber disarray. These include decrease or loss of labeling of intercalated discs and Z bands, longitudinal arrangement of desmin intermediate filaments, and focal intense, granular staining of myocytes [25]. Ultrastructually, malalignment of sarcomeric myosin filaments has been described in patients with hypertrophic cardiomyopathy with known genetic mutations [26].

Fibrosis - In addition to an increase in fibrosis in areas of myofiber disarray, there may be patchy interstitial fibrosis to extensive and grossly visible scars that may even be transmural [6].

Coronary Artery Abnormalities - Abnormal intramural coronary arteries, characterized by thickening of the vessel wall with a decrease in lumen size, are found within the ventricular septum in 83% of hearts, with a mean of 3 per tissue section. Intramural coronary artery thickening is more common in hearts with fibrosis than those without significant fibrosis. The vessels are dysplastic without a well developed internal elastic lamina and smooth muscle cells are in disarray.

Epicardial coronary arteries are usually normal in hypertrophic cardiomyopathy. However, the presence of a myocardial bridge over a portion of the left anterior descending artery (tunnel) has been associated with an increased risk of sudden death, especially in children.

Histologic Findings of Myomectomy Specimens - Patients with > 50 mm Hg subaortic gradient are often treated surgically with myomectomy and/or myotomy for the relief of outflow tract obstruction. In a study of 89 myomectomy specimens from patients with hypertrophic cardiomyopathy, myofiber disarray was present in 58%, generally in the deepest portion of the specimen. In contrast, myofiber disarray is present in a smaller proportion of endomyocardial biopsies, secondary to sampling error [28]. Other histologic features of hypertrophic cardiomyopathy that may be seen in myomectomy specimens include intramural artery thickening and endocardial fibrous plaque [28].

Arrhythmogenic Right Ventricular Dysplasia

Definition -

Right ventricular cardiomyopathy has many synonyms and related terms, including right ventricular dysplasia, arrhythmogenic right ventricular dysplasia, arrhythmogenic right ventricular dysplasia-cardiomyopathy, parchment heart, partial absence of the right ventricle, and Uhl's anomaly. The current preferred term is arrhythmogenic right ventricular dysplasia-cardiomyopathy [1,29].

The definition of arrhythmogenic right ventricular dysplasia is based on pathologic criteria of "transmural fibrofatty replacement of the right ventricular myocardium" [30]. As will be pointed out, the pathologic criteria are not yet uniformly accepted, as is the case for most types of cardiomyopathy.

There is ongoing debate about the nature of arrhythmogenic right ventricular dysplasia. Originally considered a genetically determined congenital malformation, it may represent a healed form of myocarditis.

Pathologic Features

Gross Findings - The heart is generally normal in size or slightly enlarged. The right ventricle is dilated, often only focally, and there is usually an area of myocardial thinning to 2 mm or less. Aneurysmal thinning may occur anywhere in the right ventricle, especially the right ventricular outflow tract (infundibulum), apex, and posterobasal segment. The epicardial fat may be thickening over the affected areas. The left ventricle is normal in two-thirds of cases, although subepicardial scars may be present, most frequently in the posterior wall. The presence of gross left ventricular enlargement identifies a subset of patients who tend to be older and develop heart failure more frequently than patients with grossly normal left ventricles.

Histologic Findings - The histologic features of arrhythmogenic right ventricular dysplasia include fibrosis, fat, and inflammation. Fat infiltration of the right ventricular myocardium is usually considered a sine qua non for the diagnosis of arrhythmogenic right ventricular dysplasia. Fibrosis, on the other hand, is only sometimes considered a required feature. The disease has been pathologically subclassified based on the proportion of fat and fibrous tissue present. Italian investigators recognize a lipomatous and fibrolipomatous pattern [32,33] and Lobo et al. add a third type, in which there is an absence of myocardium with apposition of endocardium and epicardial tissue [31].

The autopsy diagnosis of arrhythmogenic right ventricular dysplasia should not be made entirely based on the presence of fat. Fat infiltration of the anterior wall of over 50% of myocardial area is not unusual in hearts from trauma victims, especially in the anterior wall near the apex. Thin myocardial fascicles dispersed within epicardial fat (in the absence of fibrosis) is also a normal finding and not pathognomonic for cardiomyopathy. The hallmark of arrhythmogenic right ventricular dysplasia is transmural fat infiltration accompanied by fibrosis and thinning of the ventricular wall. The myocytes in the affected regions typically possess a characteristic bubbly or foamy cytoplasm which, on ultrastructural analysis, represents marked mitochondrosis.

Massive fat infiltration of the myocardium, with a thickened ventricular wall (>4 mm) instead of a thin one, has been associated with sudden death. Massive fat infiltration of the myocardium should probably be considered separately from arrhythmogenic right ventricular dysplasia, because the right ventricle is generally thicker than normal, and cardiac dilatation is not a prominent feature.

Lymphocytic infiltrates are frequently found in affected areas of myocardium, and have been described in up to 70% of cases of arrhythmogenic right ventricular dysplasia [34].

With histologic evaluation of autopsy cases, it has become evident that arrhythmogenic right ventricular dysplasia is a biventricular disease. Subepicardial scars, fatty infiltrates, or inflammatory foci are present in approximately 75% of left ventricles, usually in the lateral wall. Patients with gross or microscopic evidence of left ventricular involvement are more likely to have ventricular arrhythmias and enlarged hearts as compared to those patients with isolated right ventricular involvement.

The endomyocardial biopsy diagnosis of arrhythmogenic right ventricular dysplasia is hampered by sampling error, and a negative biopsy does not exclude the diagnosis. If excess fat and fibrous tissue is present in an endomyocardial biopsy, the diagnosis may be suggested in the appropriate clinical setting. By morphometric study, the degree of fat in endomyocardial biopsies is greater in patients with arrhythmogenic right ventricular dysplasia than control patients and those with dilated

cardiomyopathy. Interstitial fibrosis is also increased, but similar to that seen in dilated cardiomyopathy [35].

Table 4. Differential features, hypertrophic vs. dilated cardiomyopathy

	Dilated cardiomyopathy	Hypertrophic cardiomyopathy
Incidence (yearly)	6/100,000	2.5/100,000
Mean age at diagnosis	45	30's
Familial	7 - 20%	50 - 60%
Genetic basis	Unknown; rarely dystrophin gene abnormality	Beta myosin heavy chain and others
Viral etiology	10 - 20%	None implicated
Functional defect	Systolic	Diastolic
LV chamber size	Increased	Decreased or normal
LV mass	Increased	Greatly increased
Sudden death	20%	40%
At presentation	3%	20%
Congestive heart failure	>95%	10%
Arrhythmias	Common	Common
10 year survival	15%	60%

References

1. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996; 93:841-2.
2. Waller BF. Pathology of the cardiomyopathies. J Am Soc Echocardiogr 1988; 1:4-19.
3. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994; 331:1564-75.
4. Felker GM, Hu W, Hare JM, et al. The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients. Medicine (Baltimore) 1999; 78:270-83.
5. Kasper EK, Agema WR, Hutchins GM, et al. The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients. J Am Coll Cardiol 1994; 23:586-90.
6. Roberts WC, Ferrans VJ. Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. Hum Pathol 1975; 6:287-342.
7. Keren A, Billingham ME, Weintraub D, et al. Mildly dilated congestive cardiomyopathy. Circulation 1985; 72:302-9.
8. Atkinson JB, Virmani R. Congestive heart failure due to coronary artery disease without myocardial infarction: clinicopathologic description of an unusual cardiomyopathy. Hum Pathol 1989; 20:1155-62.
9. Ferrans VJ. Pathologic anatomy of the dilated cardiomyopathies. Am J Cardiol 1989; 64:9C-11C.
10. Davies MJ, McKenna WJ. Dilated cardiomyopathy: an introduction to pathology and pathogenesis. Br Heart J 1994; 72:S24.
11. Unverferth DV, Baker PB, Swift SE, et al. Extent of myocardial fibrosis and cellular hypertrophy in dilated cardiomyopathy. Am J Cardiol 1986; 57:816-20.
12. Tazelaar HD, Billingham ME. Leukocytic infiltrates in idiopathic dilated cardiomyopathy. Am J Surg Pathol 1986; 10:405-12.
13. Schaper J, Froede R, Hein S, et al. Impairment of the myocardial ultrastructure and changes of the cytoskeleton in dilated cardiomyopathy. Circulation 1991; 83:504-14.
14. Rowan RA, Masek MA, Billingham ME. Ultrastructural morphometric analysis of endomyocardial biopsies. Idiopathic dilated cardiomyopathy, anthracycline cardiotoxicity, and normal myocardium. Am J Cardiovasc Pathol 1988; 2:137-44 [and molecular data Br Heart J 1994; 72:S25-29].
15. Arbustini E, Diegoli M, Fasani R, et al. Mitochondrial DNA mutations and mitochondrial abnormalities in dilated cardiomyopathy. Am J Pathol 1998; 153:1501-10.
16. Frustaci A, Magnavita N, Chimenti C, et al. Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction. J Am Coll Cardiol 1999; 33:1578-83.
17. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA 2000; 283:1183-8.
18. Maron BJ, Bonow RO, Cannon RO, et al. Hypertrophic cardiomyopathy. N Engl J Med 1987; 316:780-789.
19. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation 1995; 92:785-89.
20. Roberts CS, Roberts WC. Hypertrophic cardiomyopathy as a cause of massive cardiomegaly (greater than 1,000 g). Am J Cardiol 1989; 64:1209-10.
21. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of

hypertrophy. A review. Prog Cardiovasc Dis 1985; 28:1-83.
22. Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: an introduction to pathology and pathogenesis. Br Heart J 1994; 72:S2-3.
23. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation 1979; 4:689-706.
24. Maron BJ, Anan TJ, Roberts WC. Quantitative analysis of the distribution of cardiac muscle cell disorganization in the left ventricular wall of patients with hypertrophic cardiomyopathy. Circulation 1981; 63:882-94.
25. Francalanci P, Gallo P, Bernucci P, et al. The pattern of desmin filaments in myocardial disarray. Hum Pathol 1995; 26:262-6.
26. Muraishi A, Kai H, Adachi K, et al. Malalignment of the sarcomeric filaments in hypertrophic cardiomyopathy with cardiac myosin heavy chain gene mutation. Heart 1999; 82:625-9.
27. Maron BJ, Wolfson JK, Epstein SE, et al. Intramural (small vessel) coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986; 8:545-57.
28. Tazelaar HD, Billingham ME. The surgical pathology of hypertrophic cardiomyopathy. Arch Pathol Lab Med 1987; 111:257-60.
29. Corrado D, Fontaine G, Marcus FI, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. Circulation 2000; 101:E101-6.
30. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994; 71:215-8.
31. Lobo FV, Heggtveit HA, Butany J, et al. Right ventricular dysplasia: morphological findings in 13 cases. Can J Cardiol 1992; 8:261-8.
32. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation 1996; 94:983-91.
33. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988; 318:129-33.
34. Burke AP, Farb A, Virmani R. Arrhythmogenic right ventricular dysplasia-cardiomyopathy: a form of healing myocarditis? J Am Coll Cardiol 1996; 27:399A.
35. Burke AP, Farb A, Tashko G, et al. Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium. Are they different diseases? Circulation 1998; 97:1571-80.