Stereotypical Pathologic Features of the Failing Heart

Hypertrophy of cardiac muscle is a fundamental response to any condition that causes the heart to work harder. It can arise from a pressure overload state (e.g., systemic hypertension or aortic stenosis), a volume overload state (e.g., mitral or aortic regurgitation), a state in which substantial ventricular muscle has been lost to infarcts and the remaining muscle must do more work, or conditions in which the muscle itself has been injured directly and cannot pump blood to meet metabolic demands without undergoing some compensatory changes. In hypertrophy, sarcomeres can be added both in series and in parallel orientations depending, in part, on the extent of ventricular dilatation that may also occur. Much progress has been made in identifying chemical and mechanical signals, receptors for these signals, and signal transduction pathways that mediate the hypertrophic response. These include stretch, β-adrenergic pathways, and pathways activated by various growth factors including angiotensinII, endothelin, and growth hormone.

When the hypertrophic response is sufficient to meet metabolic demands, then no significant ventricular dilatation occurs (unless the hypertrophic response is initiated by an acute volume overload state) and cardiac myocytes exhibit no structural abnormalities other than the obvious fact that they are larger. However, if the hypertrophic response is inadequate to meet metabolic demands, either because the “demands” have increased (for example, hypertension has become more severe) or the demands are the same but the muscle has become more injured or diseased, then ventricular dilatation occurs. Ventricular dilatation is a fundamental response of the failing heart. Dilatation is an adaptive response in that it increases contractility via the Frank-Starling mechanism.

Ventricular dilatation may convert a thickened, hypertrophied ventricular wall into a “normal” appearing or even thinned wall. However, because hypertrophy generally precedes dilatation and the heart typically does not dilate significantly until the “compensated” hypertrophic response fails to meet peripheral demands, there is almost always a considerable amount of hypertrophy in chronically failing hearts.

Although it is clear that, particularly early on in the remodeling process, hypertrophy and dilatation are adaptive responses to injury that enhance function, current evidence suggests that progressive remodeling characterized by ongoing hypertrophy and dilatation is highly maladaptive both in terms of contractile function and electrophysiology. Medical therapy, notably with angiotensin converting enzyme inhibitors, can be effective in limiting the remodeling that follows acute myocardial infarction and in preventing progression of remodeling in patients with asymptomatic ventricular dysfunction. Now that mortality from acute myocardial infarction has dropped significantly, heart failure has emerged as the major cause of cardiovascular morbidity and mortality in the US. Mechanisms that mediate remodeling and the pathophysiological effects of remodeling on cardiac function are subjects of intense interest in the search for ways to better treat heart failure and limit its progression.
Chronically failing ventricular myocytes exhibit structural alterations characterized by loss of myofibrils. It does not seem to matter whether cellular dysfunction is caused by repetitive bouts of sub-lethal ischemia, chronic pressure overload (in hypertension or in valvular disease such as aortic stenosis), volume overload (in mitral regurgitation, for example), or primary injury of the heart muscle (in the cardiomyopathies). In each case, there is diminished contractile function and pathologically one sees the same basic picture: myocytes with a substantial loss of sarcomeres and a corresponding increase in cytosol and often an increase in intracellular glycogen stores. These changes are probably reversible and likely occur as a result of perturbations in myocytes protein synthesis and degradation dynamics. They may represent a survival response in that energy requirements are probably diminished in proportion to the loss of contractile organelles. An important diagnostic point is that it is usually impossible to determine the etiology of heart failure by histologic examination of the myocardium. There are some exceptions in which distinctive histologic features allow identification of a specific cause (e.g., heart failure in hemochromatosis in which failing myocytes are filled with iron). In the great majority of patients with congestive heart failure, however, the pathologic picture must be regarded as a final common pathway type of response of the myocytes to a variety of injurious agents.

Pathology of Major Forms of Heart Failure

Heart Failure Associated with Coronary Artery Disease and Hypertension: By far, the two commonest forms of heart disease that lead to heart failure are ischemic heart disease (narrowing and occlusion of the coronary arteries due to atherosclerosis) and systemic hypertension (high blood pressure). In each of these cases, the heart muscle is not primarily diseased. Rather it is injured as a consequence of a disease process elsewhere – in the coronary arteries leading to inadequate blood flow to the heart muscle in the case of ischemic heart disease, and in the peripheral blood vessels leading to increased vascular resistance in the case of hypertension. Heart failure in the setting of coronary artery disease is usually attributable to a combination of permanent loss of muscle with replacement by scar tissue (myocardial infarction or heart attack) and chronic, sub-lethal injury of remaining viable muscle due to inadequate blood flow. This can lead to a complex clinical and pathological conditions known as ischemic cardiomyopathy (cardio-myo-pathy means: heart-muscle-disease) in which the heart exhibits areas of scarring as well as extensive remodeling of the non-infarcted segments which first undergo a hypertrophic response and subsequently become dilated and exhibit degenerative features of myofibrillar loss. In hypertensive cardiomyopathy, the increased work load on the heart causes an initial compensatory hypertrophic phase which may be followed by dilatation if the individual manifests overt heart muscle. The gross and microscopic pathology of hypertensive cardiomyopathy are not specifically different from that of idiopathic dilated cardiomyopathy (see below).

Primary Cardiomyopathies

The cardiomyopathies are a diverse group of primary diseases of heart muscle. A common definition: "a disease of myocardium not associated with hypertension, valvular disease, congenital abnormalities or coronary artery disease".

The cardiomyopathies are usually classified according to 4 major physiological and pathoanatomical groupings: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy
(HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy. In a strict sense, only DCM, HCM and ARVC are actual primary diseases of cardiac myocytes. In the restrictive cardiomyopathies, infiltration of the myocardial interstitium by substances such as amyloid, or fibrotic thickening of the endocardium cause myocardial dysfunction by altering the compliance of the ventricular wall. Although restrictive cardiomyopathies are not diseases of cardiac myocytes per se, they are included among the cardiomyopathies because they behave clinically as a cardiomyopathic process and are not associated with coronary, valvular, hypertensive or congenital forms of heart disease.

**Dilated cardiomyopathy**

The terms "dilated cardiomyopathy" and "congestive cardiomyopathy" are used interchangeably to refer to this diverse group of myocardial diseases. Many etiologies may be associated with the clinical and morphological expression of dilated cardiomyopathy and in most cases the cause is unknown (idiopathic dilated cardiomyopathy).

Grossly, the heart is large and flabby due to marked dilatation of all four chambers. Although the ventricle walls may appear thinned, hypertrophy (increased muscle mass) is invariably present. The ventricular endocardium often contains discrete collagenous patches (organized mural thrombi). Typically, the coronary arteries and valves are normal. Transmural fibrosis is absent. Microscopically, the changes are non-descript; myocyte hypertrophy and interstitial fibrosis are always present. At end-stage, seen at autopsy, inflammatory cells are absent. These histological features are entirely non-specific and do not shed light on pathogenic mechanisms.

The morphologic appearance of the heart at autopsy or transplantation in patients with dilated cardiomyopathy is the end-stage of a final common pathway caused by a variety of known and unknown etiologic factors. Many genetic, infectious, nutritional and cardiotoxic agents have been implicated in the pathogenesis of dilated cardiomyopathy.

Genetic factors play a major role. Among patients with idiopathic dilated cardiomyopathy, at least 35% have a familial disease. The proportion may be even greater because incomplete penetrance often makes it difficult to identify early or latent disease in family members. Most familial cases seem to be transmitted as an autosomal dominant trait, but autosomal recessive, X-linked recessive, and mitochondrial inheritance patterns have all been described.

Mutations in several known genes including those encoding dystrophin, -sarcoglycan, troponin T, -myosin heavy chain, actin, lamin A/C, and desmin have been identified to cause a dilated cardiomyopathy phenotype. Mutations in any given gene account for only a very small percentage of DCM cases. Allelic variation is very large. Although identification of specific genetic factors contributing to dilated cardiomyopathy is far from complete and elucidation of mechanisms by which cardiac myocytes fail requires further clarification, some general themes have emerged. A current hypothesis holds that defects in force transmission lead to development of a dilated, poorly contracting heart. Normal cardiac function requires generation of force by sarcomeres and transmission of that force to the cytoskeleton and extracellular matrix. Thus, stabilization of sarcomeres mediated by attachments of the actin cytoskeleton to the extracellular matrix via dystrophin and -sarcoglycan may be perturbed by mutations in genes encoding actin or the dystrophin/sarcoglycan complex. Mutations in the cytoskeletal protein desmin may act similarly. Interestingly, mutations in proteins such as actin, troponin T, and -myosin heavy chain may produce either DCM or HCM clinical phenotypes,
perhaps depending on whether they produce a defect in force generation (which, as discussed below, has been implicated in hypertrophic cardiomyopathy) or force transmission. For example, actin mutations associated with hypertrophic cardiomyopathy have been localized to a portion of the molecule near a myosin-binding site which could impair sarcomere function, whereas dilated cardiomyopathy-associated mutations in actin are located within the region that binds to the dystrophin sarcoglycan complex. Lamins A and C are intermediate filament proteins associated with the inner surface of the nuclear envelope. It is not clear how mutations here may produce dilated cardiomyopathy. It has been suggested that defects in lamin A/C could make the nucleus more vulnerable to mechanical stress and, thereby, cause myocyte death.

Many patients with the initial clinical manifestation of dilated cardiomyopathy undergo endomyocardial biopsy. In most cases, the biopsy reveals non-specific histological features, but in a few patients, lymphocytic infiltrate is seen. In some patients, there is a history of an antecedent viral infection, causing speculation that viral myocarditis or post-viral autoimmune inflammation may be the etiology of some (? many) cases of idiopathic dilated cardiomyopathy. There is only limited evidence of clinical improvement after therapy with anti-inflammatory and immunosuppressive drugs in individuals with inflammatory biopsies.

**Hypertrophic cardiomyopathy**

*Hypertrophic cardiomyopathy* is characterized by left ventricular hypertrophy and an increased resistance to diastolic filling (decreased compliance). These structure/function changes occur do not arise in response to an identifiable stressor (e.g., hypertension or aortic stenosis). Rather, they develop as an intrinsic feature of the primary heart muscle disease. The ventricular septum is often but not always disproportionately thickened. During systole, contraction of the thickened ventricular septum may obstruct outflow just below the aortic valve (subaortic stenosis).

HCM is usually manifest clinically in young adults of either sex, but all age groups can be affected. Signs and symptoms include shortness of breath, angina, fatigue, syncope (fainting) and palpitations. Sudden death due to arrhythmias of unknown mechanisms is very common.

The clinical picture of hypertrophic cardiomyopathy may be caused by mutations in more than 20 genes. By far, most cases involve mutations in genes encoding proteins of the sarcomere. Mutations in 2 genes, those encoding the $\alpha$-myosin heavy chain and myosin binding protein C, account for $\sim$80% of cases. Mutations in 3 others, troponin T, cardiac troponin I and $\alpha$-tropomyosin-1 (components of the troponin complex) account for most of the remaining cases. However, like DCM, there is marked allelic heterogeneity in HCM such that most mutations occur “privately” or at frequencies of <1%. Thus, hundreds of different mutations, mostly missense, have been identified. In addition, mutations in several non-sarcomeric protein genes have been linked to the clinical phenotype of HCM although these account for very few cases. And, as noted earlier in discussing the genetics of DCM, it is becoming increasingly clear that different mutations in the same gene can give rise to various clinical phenotypes of DCM or HCM.

Despite great advances in identifying the genetic causes of HCM, how the mutations cause clinical and pathologic phenotypes remains poorly understood. In general, it is thought that the mutant protein is incorporated into the sarcomere, where it acts in a dominant-negative fashion to cause a loss of sarcomeric function. *This proposed mechanism has led to the hypothesis that HCM is related to defects in force generation owing to altered sarcomeric function. This*
suggests that hypertrophy occurs as a compensatory response. Other mutations, such as those involving myosin light chain and α-tropomyosin-1 genes, may actually enhance contractility and, thereby, lead to hypertrophy. Still others (e.g., mutations in the myosin-binding protein C gene) may produce proteins that do not become incorporated into sarcomeres. These might lead to hypertrophy through a lack of the functional protein, rather than by a dominant-negative effect.

Because of the known risk of sudden death in HCM, there have been many attempts to use genetics as a means of risk stratification. Overall, the results have been disappointing although some correlations have been recognized. For example, selected mutations in β-myosin heavy chain and troponin T genes involve a high likelihood of sudden death. In the case of the β-myosin heavy chain mutations, the risk of sudden death correlates with the amount of hypertrophy, whereas troponin T mutations, which are also linked to sudden death, produce minimal or no hypertrophy. HCM in patients with myosin-binding protein C mutations is usually benign clinically and is associated with slowly progressive hypertrophy developing late in life. A few patients (2-5%) have mutations in 2 genes. This is generally associated with earlier onset and a more severe clinical phenotype.

The heart in HCM is always enlarged, but the degree of hypertrophy is different in different genetic forms. The left ventricle wall is thick, and its cavity is small, sometimes being reduced to a slit. Papillary muscles and trabeculae carneae are prominent and encroach on the ventricular lumen. More than half of cases exhibit asymmetric hypertrophy of the interventricular septum, with a ratio of the thickness of the septum to that of the left ventricular free wall greater than 1.5. There are some rare genetic forms of HCM in which only the apical portion of the left ventricle or papillary muscles are selectively hypertrophied. Often, the thickened, hypertrophied interventricular septum bulges into the left ventricular outflow tract early in ventricular systole, causing subvalvular obstruction of the aortic outflow tract. In this situation, an endocardial mural plaque is typically seen in the outflow tract, corresponding to the contact point where the anterior mitral valve leaflet impinges on the septal wall of the outflow tract during systole. Both atria are commonly dilated.

The most notable histologic feature of HCM is myofiber disarray, which is most extensive in the interventricular septum. Instead of the usual parallel arrangement of myocytes into muscle bundles, myofiber disarray is characterized by an oblique and often perpendicular orientation of adjacent hypertrophic myocytes. By electron microscopy, myofibrils and myofilaments within individual myocytes are also disorganized. Such structural disarrangements are also frequently present in infants with congenital heart defects and can be observed under a variety of circumstances. However, they are always extensive in HCM and are not as widespread in other situations. There is usually hyperplasia of interstitial cells, and intramural coronary arteries may become thick and cellular.

Many patients with HCM have few if any symptoms, and the diagnosis is commonly made during screening of the family with an affected member. Despite a lack of symptoms, such persons may be at risk for sudden death, particularly during severe exertion. In fact, unsuspected HCM is a commonly found at autopsy in young competitive athletes who die suddenly. Clinical recognition of HCM can occur at any age, often in the third, fourth, or fifth decade of life, but the disorder also is encountered in the elderly (mainly in patients with myosin binding protein C mutations). Some patients with HCM become incapacitated by cardiac symptoms, of which dyspnea, angina pectoris, and syncope are most common. The clinical course tends to remain stable for many years, although eventually the disease can progress to congestive heart failure.
Despite the fact that mutant proteins impair the sarcomere, contractile function in HCM tends to be hyperdynamic. Ejection fractions are typically very high and most of the stroke volume is ejected during early systole. The most prominent dysfunctional aspect of HCM is decreased left ventricular compliance (diastolic dysfunction), which results in increased end-diastolic pressure. Mitral regurgitation is also seen in many HCM patients. These features contribute to the atrial dilation commonly seen in HCM. In one fourth of patients, functional obstruction of the left ventricular outflow tract occurs near the end of systole, resulting in a pressure gradient between the apex and the subvalvular region of the left ventricle.

HCM responds paradoxically to pharmacologic interventions. Heart failure from other causes is typically treated with cardiac glycosides to increase myocardial contractility and with diuretics to reduce intravascular volume. In HCM, these drugs aggravate symptoms. The most efficacious treatment of HCM is \( \beta \)-adrenergic blockers and calcium channel blockers, which reduce contractility, decrease outflow-tract obstruction, and may improve left ventricular relaxation during diastole. Surgical removal of a portion of the hypertrophic septum or injection of ethanol into a septal artery to cause localized infarction has been successful in relieving symptoms of obstruction but seems to have no impact on the risk of sudden death.

**Arrhythmogenic right ventricular cardiomyopathy**

ARVC affects roughly 1 in 5,000 individuals. It occurs most commonly in Mediterranean countries where it is a leading cause of sudden death in young people (<35 years of age). ARVC is associated with serious arrhythmias and/or sudden death which may occur early in the disease before significant structural remodeling and contractile dysfunction develop. It typically affects the right ventricular free wall, although left dominant and bi-ventricular forms are being recognized increasingly. The characteristic pathologic features are degeneration of cardiac myocytes and replacement by fat and fibrous tissue, but the extent of this change can be quite variable and it is not necessarily conspicuous in patients who die suddenly.

ARVC is a familial disease, usually inherited in a dominant pattern. Its true incidence is probably underestimated because of highly variable penetrance, age-related progression, and large phenotypic variation. The diagnosis can be difficult to make and requires analysis of various clinical criteria which, although relatively specific, are not very sensitive. Mutations in genes encoding proteins in desmosomes, cell-cell adhesion organelles, can be identified in nearly half of individuals who fulfill these criteria. These include genes for desmosomal adhesion molecules such as desmoglein-2 and intracellular desmosomal proteins including plakoglobin, desmoplakin and plakophilin-2 which form a complex that links the adhesion molecules to the desmin cytoskeleton in cardiac myocytes. Desmosomes are particularly abundant in heart and skin, two organs that experience the greatest mechanical burden, and mutations in desmosomal genes generally give rise to cutaneous and/or cardiac disease depending on the tissue-specific expression pattern of the mutant isoform. It is generally thought that abnormal biomechanical behavior plays an important role in disease pathogenesis but how this might cause the clinical and pathologic features of ARVC is poorly understood.
Restrictive cardiomyopathies

Restrictive cardiomyopathy describes a group of diseases in which myocardial or endocardial abnormalities limit diastolic filling, while contractile function remains normal. It is the least common category of cardiomyopathy in Western countries, although in some less-developed regions (e.g., parts of equatorial Africa, South America, and Asia), endomyocardial disease related to parasitic infections leads to many cases of restrictive cardiomyopathy.

Restrictive cardiomyopathy is caused by (1) interstitial infiltration of amyloid, metastatic carcinoma, or sarcoid granulomas; (2) endomyocardial disease characterized by marked fibrotic thickening of the endocardium; (3) genetic and storage diseases, including hemochromatosis and desmin-related cardiomyopathies; and (4) markedly increased interstitial fibrous tissue. The pathophysiologic consequence is a pre-load-dependent state, characterized by defective diastolic compliance, restricted ventricular filling, increased end-diastolic pressure, atrial dilation, and venous congestion. In many respects, these hemodynamic changes are similar to the consequences of constrictive pericarditis. Many cases of restrictive cardiomyopathy are classified as idiopathic, with interstitial fibrosis as the only histologic abnormality. The disease almost invariably progresses to congestive heart failure, and only 10% of the patients survive for 10 years.

Amyloidosis: The heart is affected in most forms of generalized amyloidosis. In fact, restrictive cardiomyopathy is the most common cause of death in AL amyloidosis of plasma cell dyscrasias. Amyloid infiltration of the heart results in cardiac enlargement without ventricular dilation, and the gross appearance of the heart may resemble that of hypertrophic cardiomyopathy. Ventricular walls are typically thickened, firm, and rubbery. Microscopically, amyloid accumulation is most prominent in interstitial, perivascular, and endocardial regions. Endocardial involvement is common in the atria, where nodular endocardial deposits often impart a granular appearance and gritty texture to the endocardial surface. Amyloid deposits also can cause thickening of cardiac valves. In rare cases, amyloid deposition within the walls of intramural coronary arteries narrows the lumens and causes ischemic injury.

Desminopathies: Desmin is the intermediate filament protein in cardiac, striated and smooth muscle. Desmin filaments bind to desmomes at intercalated disks and span the length of the cardiac myocyte by binding to Z-disks of sarcomeres and other intracellular organelles. Numerous mutations in desmin have been described in patients with skeletal and cardiomyopathies; most are inherited as autosomal dominant traits. The heart disease usually falls in the clinicopathologic spectrum of restrictive cardiomyopathies characterized by ventricular wall thickening, loss of ventricular compliance and diastolic dysfunction. In many forms, the mutant protein is expressed and it presumably interferes with normal desmin filament production. Large intracellular aggregates of refractile material can be seen by light microscopy and represent tangled masses of misfolded desmin filaments.

Valvular Heart Disease

Abnormalities of the structure and function of the cardiac valves can lead to heart failure. There are two types of valvular abnormalities. A stenotic valve does not open properly and offers resistance to blood flow across it, thus creating pressure overload. Structural features correlated with valvular stenosis include fusion of the lines of closure of the value leaflets (the
commissures), rigidity of the leaflets (fibrosis or calcification), and congenital malformations creating inherently stenotic valves.

An incompetent, insufficient, or regurgitant (all synonymous) valve does not close properly and allows blood to leak back across it, thus creating volume overload. Structural or functional abnormalities of the leaflets, valve ring (annulus), or subvalvular apparatus (chordae and papillary muscles) may all contribute.

Aortic stenosis may be due to commissural fusion and/or calcification and rigidity of the cusps. Rheumatic aortic stenosis used to be very common but is now much less so. In this condition, the cusps are diffusely thickened by fibrous tissue and are often calcified. Commissural fusion is usually present. A rheumatic aortic valve may be both stenotic and incompetent. Rheumatic aortic valve disease is virtually never isolated but co-exits with rheumatic mitral valve disease. Isolated or pure aortic stenosis (without abnormalities of other valves) is generally due to 2 other major causes (described below).

Bicuspid aortic valve is a common congenital lesion (up to 2% of the population; men > women). The orifice of a normal (3-cuspid) aortic valve is round and blood flows through it in a smooth, laminar fashion. In contrast, the orifice of a congenitally bicuspid valve is shaped like a football and this creates turbulence when blood flows across it. Turbulence causes chronic endothelial injury ultimately resulting in fibrosis and calcification of the cusps but without commissural fusion. This eventually leads to aortic stenosis and LV pressure overload. The bicuspid valve may also become incompetent if the calcified, fibrotic cusps become fixed in an open position.

Senile calcific aortic stenosis is a poorly understood degenerative condition of elderly individuals that affects three cuspid aortic valves. The cusps become rigidly fibrotic and heavily calcified on the aortic side of the valve and in the sinuses of Valsalva. There is no commissural fusion. Regurgitation is uncommon.

Aortic insufficiency may be due to dilatation of the aortic root which separates the cusps such that they are unable to contact each other and seal properly. AI due to this mechanism is seen in Marfan’s syndrome. Destruction or perforation of an aortic valve cusp due to endocarditis can also lead to aortic valvular regurgitation. Aortic regurgitation in rheumatic valve disease occurs as a result of cusp retraction or distortion preventing coaptation of the cusps. AI may also be caused by prolapse of an aortic valve cusp because of loss of support from above (e.g., after dissection of the ascending aorta) or loss of support from below (e.g., with a high ventricular septal defect).

Most cases of mitral stenosis are caused by rheumatic valve disease but this is much less common than it used to be because the incidence of acute rheumatic fever has been so low for many decades. Other causes of mitral stenosis are uncommon.

Mitral regurgitation may be due to conditions which affect, singly or in combination, the mitral annulus, leaflets, or subvalvular apparatus. Extreme dilatation of left ventricle and mitral annulus may lead to mitral regurgitation even though the leaflets and subvalvular apparatus are anatomically normal. Mitral regurgitation may be associated with perforation or destruction of a leaflet caused by infective endocarditis. Mitral valve regurgitation may also be precipitated by rupture of a papillary muscle following acute myocardial infarction or by ischemic dysfunction of the papillary muscles without frank rupture. Severe mitral regurgitation causes profound volume overload and can lead to rapid development of heart failure.