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The Value of a Heart Biopsy

By KENNETH LEE BAUGHMAN, M.D.

Despite advances in the diagnosis and treatment of patients with cardiomyopathy, the prognosis remains poor. The etiology of dilated cardiomyopathy is often unknown and is assumed to be "idiopathic" or "viral;" however, only 50% of dilated cardiomyopathies are idiopathic and a small proportion of patients with non-ischemic cardiomyopathy have ventricular dysfunction proven to be viral in origin. Determination of the etiology of a cardiomyopathy is important because it influences not only prognosis, but also medical and surgical therapy (Figure 1).[1] Just as left heart catheterization and coronary angiography are critical to understanding the pathophysiology of valvular and coronary artery disease, the myocardial biopsy is likely to become important in our attempts to unlock the mystery of heart muscle disorders.

A diagnosis of dilated cardiomyopathy does not always require heart biopsy

Patients with dilated cardiomyopathy can often have their diagnosis made, or at least strongly suspected, by a careful history, directed physical examination, limited blood work, transthoracic echocardiography and, in appropriate candidates, cardiac catheterization and coronary angiography.

Guidelines must be established in order to propose a diagnosis by history alone.[2] Hypertensive cardiomyopathy is suspected in patients who have had hypertensive crises, blood pressures > 200 mm Hg, or poor blood pressure (BP) control over a number of years. Ischemic cardiomyopathy requires documentation of a myocardial infarction (MI) with electrocardiographic changes and enzymatic elevations, a history of cardiac catheterization with a > 50% narrowing of at least 1 coronary vessel, or prior coronary bypass graft surgery. Many patients believe they have had a "heart attack" when, in fact, they were admitted for decompensated congestive heart failure. Congenital abnormalities are usually more easily identified by history, but must be confirmed. Familial cardiomyopathy may account for up to 30% of patients with dilated cardiomyopathy and can be diagnosed if first-degree relatives have presented with dilated cardiomyopathies and no other etiology is discovered. A diagnosis of peripartum cardiomyopathy is made when a patient has no preexisting heart abnormality, no other cause of dilated cardiomyopathy, and presents with heart failure in the last month of pregnancy or up to 5 months postpartum.

Drugs and toxins may cause dilated cardiomyopathy. Although adriamycin usually begins to cause left ventricular (LV) functional abnormalities at 350 mg/m^2, patients with predisposing features including chest radiotherapy, cyclophosphamide (cytoxan), or a genetic predisposition may develop a cardiomyopathy with drug exposure below this amount. Generally, to suspect alcoholic cardiomyopathy requires consumption of >8 ounces of ethanol a day for at least 6 months duration. Cocaine exposure may cause cardiomyopathy or MI.

A directed physical examination may suggest, but rarely allows, a definitive determination of the cause of a cardiomyopathy. Many patients will have mitral regurgitation when they present with a dilated cardiomyopathy. This may be due to intrinsic mitral valve disease or, more often, to displacement of the papillary muscles and chordae tendeneae, preventing apposition of the mitral leaflets. Many murmurs are altered by the presence LV dysfunction. If cardiac output is diminished, the murmur of aortic stenosis is less loud. If the LV end-diastolic pressure is elevated and arterial diastolic blood pressure is low, the murmur of aortic regurgitation will be decreased in intensity and duration. Elevations of LV end-diastolic pressure may similarly modify the timing and duration of the mitral stenotic murmur. Therefore, although the physical examination can provide clues to a valvular abnormality, additional studies are often required to confirm if the abnormality that is discovered is etiologic. Arterial-venous (A-V) communications, both naturally-occurring (Rendu-Osler-Weber syndrome) or manmade through A-V fistulae, can cause heart failure and may be identified on exam. Congenital

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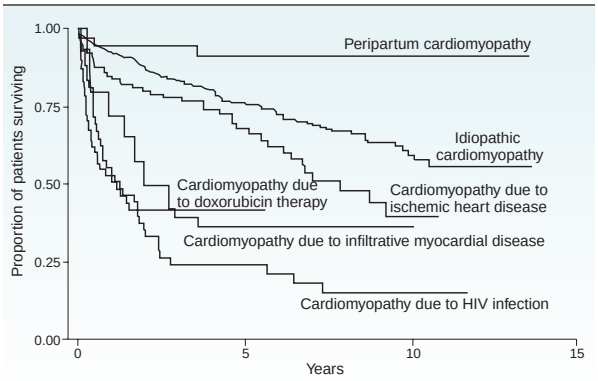
Figure 1: The importance of etiology[17]



Adjusted Kaplan-Meier estimates of survival according to the underlying cause of cardiomyopathy. Only idiopathic cardiomyopathy and cardiomyopathy due to causes where survival was significantly different from that in patients with idiopathic cardiomyopathy are shown.

abnormalities may be suggested by physical findings and central or peripheral cyanosis. Restrictive and constrictive physiology is suggested by the presence of markedly elevated jugular venous pressure and ascites with relatively little peripheral edema. Endocrinopathies may be accompanied by features of thyroid, glucocorticoid, or sympathetic nervous system excess.

The most definitive noninvasive evaluation for patients with cardiomyopathy is the transthoracic echocardiogram. This technique allows determination of the size and contractility of the left ventricle, the thickness and character of the ventricular walls, pericardial abnormalities, masses and tumors invading the heart, and primary valvular abnormalities. In addition, ischemic heart disease can be associated with the finding of two or more segments exhibiting wall motion abnormalities. Restrictive features can be suggested by the mitral valve inflow pattern and LV wall thickness.

All patients with dilated cardiomyopathy should undergo a careful history that addresses potential features that may provide a clue to their etiology (Table 1). In addition, an examination should be performed with attention to findings that may provide a clue to the cause of the heart muscle weakness. All patients should have electrocardiography to evaluate important causes of cardiomyopathy (eg, rate and possible MI), but also to evaluate rhythm, conduction abnormalities, and left and right ventricular hypertrophy. Chest x-ray may provide evidence of heart chamber size, as well as the severity of pulmonary congestion. Transthoracic echocardiography is the most beneficial noninvasive technique and should be completed on every patient presenting with heart failure. Standard hematologic and chemical blood tests important for management should be obtained. All patients should have thyroid stimulating hormone measured to rule out hyper- or hypothyroidism and most patients should have an antinuclear antibody test, since connective tissue disorders often have subtle extracardiac findings.

Table 1: Cardiomyopathy diagnosis evaluation

All patients	Selected patients
• History	• Endocrine – VMA, GH
• Examination	• Infiltrative – iron, PELP
• ECG	• Infectious – HIV
• CXR	• Coronary angiogram (age and risk factors)
• Echocardiogram	• Cath – valve/constriction
• Blood work – ANA/TSH	• Biopsy

PELP = protein electrophoresis

Table 2: Cardiomyopathy diagnoses with heart biopsy

Vascular (Fig. 2)	**Restrictive** (Fig. 3) **heart disease**	**Malignancy**	**Inflammation** (Fig. 4)
Myocardial ischemia	Amyloidosis	Adriamycin	Myocarditis
Vasospastic ischemia	Hemochromocytosis	Cytoxan	Rheumatic heart disease
		Radiation	
TTP	Hypertrophy	Carcinoid tumors	Myocardial infections (bacteria, fungi, rickettsia, etc)
	Fibrosis		
	Sarcoidosis		
	Endocardial fibroelastosis		Collagen vascular disease
			Allergy

TTP = Thrombotic thrombocytopenia purpura

Selected patients should have additional studies. Those with features suggestive of an increase in sympathetic nervous system output should be evaluated for pheochromocytoma with appropriate blood or urine studies. Patients with infiltrative cardiac diseases and/or skin color and consistency abnormalities should have iron studies to rule out hemochromatosis, or electrophoresis studies to evaluate amyloidosis. Patients presenting with cardiomyopathy and pericardial effusion associated with fever or other opportunistic infections should be evaluated for HIV. Cardiac catheterization should be performed when valvular abnormalities appear to be primary or when severe secondary mitral insufficiency is present and if there is sufficient myocardial reserve to consider surgical intervention. Coronary angiography should be performed in males >40-years-old or females >45 years who have any additional traditional risk factors for coronary atherosclerosis (eg, smoking, hypercholesterolemia, hypertension, or diabetes). The remainder of the issue will be devoted to the population that should be referred for endomyocardial biopsy.

Diagnoses possible with heart biopsy

Table 2 reveals the categories and specific etiologies that can be diagnosed by an endomyocardial biopsy. This listing is not all-inclusive; however, examples are presented below.

Vascular abnormalities

Myocardial biopsy may show evidence of myocardial ischemia (Figure 2). This is usually manifest by hemosiderin-

Figure 2: Heart biopsy – ischemic cardiomyopathy
Histologic findings include replacement fibrosis, pigment-laden macrophages, macrophage removal of dead myocytes

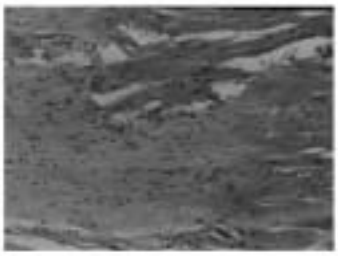
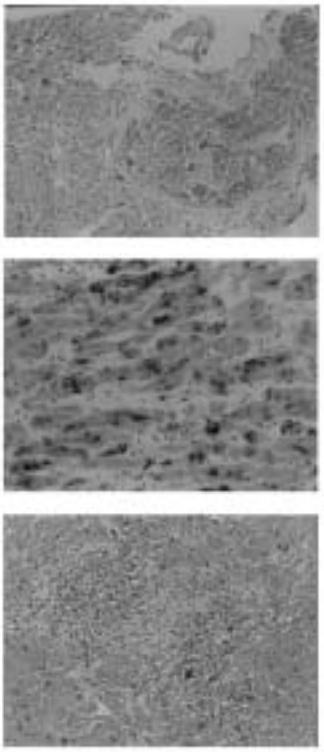


Figure 3: Endomyocardial biopsy – restrictive heart disease (amyloidosis, hemochromatosis, hypertrophy, fibrosis, sarcoidosis, endocardial fibroelastosis)



laden macrophages with replacement fibrosis. Replacement fibrosis is characterized by large areas of myocyte loss replaced by fibrous tissue. Vasospastic ischemia may also be evident in a no-flow/reflow pattern with contraction band necrosis. Thrombotic thrombocytopenia purpura (TTP) is also rarely diagnosed by endomyocardial biopsy and is usually evident by other hematologic parameters.

Restrictive heart disease

Myocardial biopsy consistently defines the etiology of restrictive heart disease (Figure 3). Examples are:

***Amyloidosis*:** Amyloidosis is characterized by focal or diffuse infiltration of the myocardium with amyloid protein. The amyloid may similarly involve small coronary vessels.

***Iron*:** Hemochromocytosis is characterized by the appearance of iron overload in the myocytes.

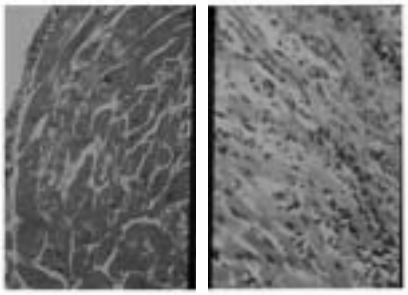
***Hypertrophy*:** Some patients develop restrictive cardiomyopathy with excessive hypertrophy alone. This is usually accompanied by interstitial fibrosis.

***Fibrosis*:** Patients may develop myocardial fibrosis, either independently or as part of a familiar disorder. This may cause a severe restrictive cardiomyopathy.

***Sarcoidosis*:** Patients with sarcoidosis may develop restrictive cardiomyopathy, dilated cardiomyopathy, valvular heart disease, conduction abnormalities, aneurysms, or pericardial disease. Noncaseating granuloma and giant cells characterize sarcoidosis with interstitial and occasionally replacement fibrosis.

***Endocardial fibroelastosis (EFE)*:** Endocardial fibroelastosis is characterized by severe thickening of the endocardium and

Figure 4: Endomyocardial biopsy – inflammatory (myocarditis, rheumatic, Infectious, collagen vascular disease, allergic-eosinophilic)



valvular structures. This may be a manifestation of prior mumps or, if exclusive to the right side of the heart, carcinoid syndrome.

Malignancy

Rarely, malignancies invade the myocardium and cause focal LV compromise. More often, the heart is damaged by chemotherapy. This includes exposure to medications such as cytoxan and adriamycin, or radiation, which causes an endothelialitis and subsequent myocardial fibrosis. Occasionally, carcinoid tumors may release cytotoxic agents that damage the endocardium and subsequently, the heart.

Inflammation

The greatest interest in the myocardial biopsy is centered on the evaluation of inflammation (Figure 4). This includes myocarditis, rheumatic heart disease, myocardial infections associated with bacteria, fungi, rickettsia, or other infectious pathogens, collagen vascular disease, or allergic inflammation.

Endomyocardial biopsy technique

The endomyocardial biopsy is performed from a central vein, preferentially the right internal jugular vein, however, the left internal jugular vein, subclavian, and both femoral veins can be utilized. The bioptome is inserted into the vein and guided through the tricuspid valve and biopsies are taken from the right side of the interventricular septum. The right ventricular free wall and pulmonary outflow track are too thin to biopsy safely since the depth of the myocardial sample is often greater than the thickness of the ventricular wall. A biopsy from these areas increases the risk for complications including myocardial perforation and pericardial tamponade.

Endomyocardial biopsy complications

The performance of an endomyocardial biopsy is associated with certain risks, in part inversely associated with the experience of the operator and the stability of the patient. In patients submitted for biopsy, approximately 6% has some complication[3] and almost half the complications occur during the introduction of the sheath into the vein (eg, incidental arterial puncture, bleeding, or rarely, pneumothorax). Exacerbation of underlying arrhythmias, conduction abnormalities, and perforation are other complications. Perforation occurs in approximately 0.5% of patients with dilated cardiomyopathy submitted to biopsy and approximately one-half of these are serious, leading to emergency pericardial drainage, either

Table 3: Myocarditis: histopathologic classification[7]

	Fulminant	Subacute	Chronic active	Chronic persistent
Onset	Distinct	Indistinct	Indistinct	Indistinct
LV function	Severe dysfunction	Moderate dysfunction	Moderate dysfunction	No dysfunction
Biopsy	Multiple foci	Active or borderline	Active or borderline	Active or borderline
Clinical history	Recovery or death	Incomplete DCM	Restrictive CM	Normal LV function
Histologic outcome	Complete resolution	Complete resolution	Giant cells-fibrosis	Ongoing

DCM = dilated cardiomyopathy

percutaneously or with oversewing the site of perforation, or death. Patients who are decompensated at the time of biopsy are at higher risk.

Evaluation of myocarditis

The greatest interest in myocardial biopsy has revolved around the diagnosis and treatment of myocarditis. Prior to 1986, there were no established histologic criteria for myocarditis. In that year, the "Dallas" criteria were established that required the presence of an inflammatory infiltrate associated with myocyte necrosis as seen under light microscopy.[4] Borderline myocarditis allows a more sparse inflammatory infiltrate and no light microscopic evidence of myocyte destruction. These criteria have been used almost exclusively by U.S. investigators since their introduction.

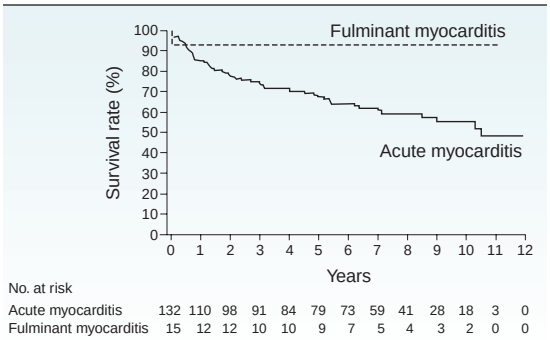
Even endomyocardial biopsy cannot be considered the "gold" standard. Utilizing one myocardial sample in patients known to have died from myocarditis, only 25% of patients would have the diagnosis of myocarditis established by histologic analysis.[5,6] With 5 myocardial biopsies, there is a two-thirds chance of making the diagnosis of myocarditis, while an additional 10%-15% would be given the diagnosis of borderline myocarditis. Therefore, using myocardial biopsy, approximately 75%-80% of those with histologic myocarditis will have the diagnosis established histologically using the "Dallas" criteria.

Clinicopathologic classification of myocarditis

Based on our experience, 4 histopathologic categories of myocarditis have been proposed: fulminant, subacute, chronic active, and chronic persistent myocarditis (Table 3).[7] These categories are pertinent only to patients who have post-viral autoimmune myocarditis and do not reflect peripartum cardiomyopathy, HIV-related myocarditis, or inflammation related to other secondary causes (eg, sarcoidosis and connective tissues disorders). These categories of myocarditis are similar to those accepted for hepatitis; they are differentiated by their symptoms at onset, degree of LV dysfunction at presentation, heart biopsy findings, and clinical, as well as histologic outcomes.

Fulminant myocarditis is characterized by a distinct onset.[8] Patients can specifically date the onset of their viral illness and congestive heart failure, both occurring within one month of presentation. Patients present with severe LV dysfunction and often, cardiogenic shock.

Figure 5: Myocarditis – fulminant vs acute[8]



Unadjusted transplantation-free survival according to clinicopathological classification. Patients with fulminant myocarditis were significantly less likely to die or require heart transplantation during follow-up than were patients with acute myocarditis (P=0.05 by the log-rank test).

Echocardiogram reveals a hypofunctional LV with thick walls, likely due to myocardial edema. Heart biopsies reveal multiple sites of myocarditis. Within 2 weeks, these patients may die or recover and have complete resolution of their histologic myocarditis with no long-term residual LV compromise (Figure 5).

Subacute myocarditis patients present with an indistinct onset and moderate LV dysfunction and dilation. Their biopsies reveal active or borderline myocarditis, but in a limited number of sites. Generally, these patients experience an incomplete recovery and usually progress to a dilated cardiomyopathy, despite histological resolution of Dallas criteria myocarditis.

Chronic active myocarditis patients present in a similar indistinct fashion and have moderate LV dysfunction. Heart biopsies reveal a combination of inflammation and scar tissue. Over time, both inflammation and scarring persist, giant cells may appear, and clinically, they develop a restrictive cardiomyopathy often requiring transplantation within 2-3 years.

Chronic persistent myocarditis also has an indistinct onset, but is unassociated with any LV compromise. Patients have complaints of palpitations or atypical chest pain without coronary disease. Biopsies reveal active or borderline myocarditis. Ventricular function remains normal throughout their course, despite persistent myocardial inflammation.

In addition to these forms of myocarditis, 2 other distinct forms of myocarditis have therapeutic implications.

Giant cell myocarditis is clinically characterized by an abrupt onset and rapid downhill course.[9,10] Patients are debilitated by resistant heart failure, conduction abnormalities, or poorly controlled arrhythmias. On biopsy, these patients have giant cells associated with myocardial inflammation and fibrosis. The natural history, if untreated, is ventricular deterioration and death, usually within 3 months.[9]

Allergic myocarditis is found in patients with eosinophilic immunologic disorders or with an allergic response, who then may develop LV compromise and dilated cardiomyopathy.[11] Myocardial biopsies are characterized by inflammatory infiltrates with a high proportion of eosinophiles. If untreated, these patients may develop severe LV compromise and/or valvular endocardial abnormalities.

Treatment of myocarditis

Standard treatment of myocarditis includes the limitation of myocardial demand, treatment of heart failure, arrhythmia, and avoidance of vascular spasm. Patients are advised to maintain activities of daily living, but not "work up a sweat." Standard heart failure management is implemented including diuretics, afterload reduction, and beta-blockers. Angiotensin-converting enzyme inhibitors may decrease the molecular signals for fibrosis, and beta-blockers may provide some protection against the toxic effects of myocardial inflammation. Vascular spasm may be promoted by viral or post-viral inflammation of the endothelium and vasospastic agents should be avoided, possibly including digitalis as well.

All other treatment of myocarditis is considered experimental and this includes immune absorption, immune stimulation, or immune suppression. In a prospective randomized trial, immunoglobulin administration has been reported to provide no significant improvement for patients with myocarditis.[12] There are no antiviral agents specific to the viruses responsible for myocarditis. In experimental studies, calcium channel blockers may provide some benefit to prevent spasm and calcium overload of the myocyte and they may contribute to viral elimination; however, there are no trials to suggest calcium channel blockers are beneficial in patients with myocarditis.

The most notable trial in the treatment of patients with myocarditis is the Myocarditis Treatment Trial published in 1995.[13] This trial evaluated over 2,200 candidates and only 10% had Dallas criteria myocarditis by endomyocardial biopsy. Of these 214 patients, 111 were randomized and two-thirds were considered to have myocarditis by an expert panel of pathologists. Patients were randomized to placebo versus prednisone and cyclosporin. Both groups displayed the same increase in ejection fraction and survival outcome. On publication of these results, enthusiasm for endo-myocardial biopsy in the United Sates dramatically diminished, since the procedure was based on use in the evaluation and treatment of myocarditis.

However, there is now new information to suggest that selected patients with myocarditis may respond to immunosuppressive therapy. With the use of polymerase chain reaction molecular cardiology techniques, investigators have demonstrated that even in the presence of viral persistence, Dallas criteria myocardial inflammation is absent.[14] European investigators utilizing other markers of immune activation, such as HLA upregulation, have identified a patient population that appears to have improved their ejection fraction and better clinical outcomes in short-term follow-up with immunosuppressive therapy.[15] Other investigators have demonstrated that patients with heart auto-antibodies respond more favorably to immunosuppressive therapy if there is no viral persistence.[14] This is in keeping with other U.S. investigators who demonstrated that patients with "borderline" myocarditis responded as well, if not better, to immunosuppressive therapy than those with established Dallas criteria myocarditis.[16]

Recognition of myocarditis is exceedingly important and underscores the role of endomyocardial biopsy as a key for diagnosis. Clearly, U.S. investigators must establish other markers of immune upregulation to adequately diagnose myocardial inflammation. Only now do we sufficiently understand the pathophysiology of myocarditis to consider treatment options. Several forms of myocarditis have distinctive histopathologic patterns and biopsy allows not only a determination of the etiology of the heart muscle deterioration, but also an appreciation for the expected natural history of the disorder. These include fulminant myocarditis, chronic active myocarditis, giant cell myocarditis, eosinophilic myocarditis, and subacute myocarditis. Patients with fulminant myocarditis should recover spontaneously without immunosuppression. Those with giant cell myocarditis, chronic active myocarditis, and eosinophilic myocarditis may respond to aggressive immunosuppressive therapy. It may be possible that a portion of the patients with subacute myocarditis who might respond to immunosuppressive therapy could be identified with molecular histopathology or circulating antibodies.

Who to biopsy?

Prospective clinical diagnoses of heart muscle disorders are notoriously inaccurate. "Tissue remains the issue" and most forms of specific heart muscle abnormalities can only be determined with myocardial biopsy. It is inappropriate to biopsy every patient presenting with cardiomyopathy. Clinicians must analyze their patients in the fashion proposed: careful history, physical examination, bloodwork, transthoracic echocardiogram, EKG, chest x-ray, and when appropriate, cardiac catheterization with coronary arteriography. Patients most appropriate for biopsy include those with:

***New LV dysfunction*:** There is little to be gained from the biopsy of patients with well-established dilated cardiomyopathies and with dramatically enlarged hearts and ejection fractions <20%.

***Rapidly worsening congestive heart failure despite therapy*:** Patients with relatively new LV compromise who fail to respond to standard medical therapy, or who deteriorate inexplicably in the face of standard medical therapy, should be submitted to myocardial biopsy. These patients may display myocarditis or evidence of an allergic reaction to current medical therapy.

***No diagnosis for cardiomyopathy despite the full evaluation*:** For patients in whom heart transplantation is being considered, determination of the etiology of the heart muscle disorder is of increased importance. Occasionally, patients will have systemic illnesses identified that may influence their candidacy for heart transplantation or alter therapy afterwards.

***Myocarditis*:** Patients with fulminant and giant cell myocarditis display typical histories and rapid cardiac deterioration. Endomyocardial biopsy establishes not only the diagnosis, but also has significant therapeutic implications. Patients with chronic active myocarditis, eosinophilic myocarditis, and subacute myocarditis have less distinct histories, but nonetheless, determination of their etiology establishes treatment options.

***Restrictive cardiomyopathy*:** Patients with restrictive verses constrictive physiology should be submitted to endomyocardial biopsy unless there is clear-cut evidence for pericardial constriction.

***Specific heart muscle disorders*:** Endomyocardial biopsy is indicated where a specific etiology is being considered and the diagnosis has not been established by other means. This may include forms of restrictive cardiomyopathy such as amyloidosis and hemochromatosis. It may also include the evaluation of patients with HIV cardiomyopathy for evidence of opportunistic infection or patients with increased wall thickness who are being evaluated for Fabry's disease. Multiple examples are evident from the specific histopathologic diagnoses possible through endomyocardial biopsy noted above.

***When catheterization is risky*:** Patients with cardiomyopathy who present with renal insufficiency or are "too ill" for a left heart catheterization may have their diagnosis established by endomyocardial biopsy. In addition, a right heart catheterization performed at the same time provides helpful information on the management of this population.

***Research*:** The number of diagnoses possible by endomyocardial biopsy will increase over time as cellular and molecular techniques advance and ultimately, will lead into genetic analysis. Endomyocardial biopsy and the study of obtained tissues will likely be the key to unlocking the mysteries of myocardial dysfunction.

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Kenneth L. Baughman, MD, received his undergraduate and medical degrees from the University of Missouri in Columbia, Missouri. He trained in internal medicine at The Johns Hopkins Hospital in Baltimore, Maryland, and subsequently was the Assistant Chief of the Osler Medical Service (chief resident). He completed his fellowship in cardiology at the Massachusetts General Hospital before returning to Johns Hopkins to join the faculty in the Division of Cardiology. Dr. Baughman initiated the medical heart failure section and heart biopsy service at Johns Hopkins and became the Director of the Division of Cardiology and E. Cowles Andrus Professor of Medicine. For over 20 years, the heart biopsy service at Johns Hopkins compiled an extensive database of diagnostic heart biopsies. These data, which included demographics, heart biopsy results, and right heart catheterization combined with long-term follow-up, have served as his "observational laboratory." Dr. Baughman came to Harvard and the Brigham and Women's Hospital to head the world-class Advanced Heart Disease Unit, which evaluates and treats patients with congestive heart failure, manages heart transplantation patients, and studies devices used in the treatment of patients with severe heart disease. Dr. Baughman has authored or co-authored over 100 peer-reviewed manuscripts, 33 book chapters, and a multitude of reviews and invited editorials. He is internationally recognized for his contributions to the area of cardiomyopathy and has lectured across the United States. Dr. Baughman is currently a Professor of Medicine in the Harvard Medical School and serves on the editorial board of the *Journal of the American College of Cardiology*.

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