Systolic heart failure: Chronic and acute syndromes

Kanu Chatterjee, MB, FRCP, FCCP, FACC, MACP; J. Eduardo Rame, MD, MPhil

Systolic heart failure is characterized by ventricular dilation and reduced ejection fraction, and this syndrome may be either chronic or acute. Left ventricular remodeling is the principal cause of progression of systolic heart failure. Acute heart failure resulting from cardiomyopathy has similar functional and morphologic abnormalities. This review discusses remodeling, initial therapy based on neurohormonal modulation, and treatment of decompensated and refractory heart failure. Diagnosis, prognosis, and management of acute myocarditis are also discussed. (Crit Care Med 2008; 36[Suppl.]:S44–S51)

**Key Words:** systolic heart failure; remodeling; myocarditis; decompensated heart failure; refractory heart failure; endomyocardial biopsy; immunosuppression therapy

Systolic heart failure (SHF), frequently referred to as heart failure with reduced ejection fraction, is defined as a clinical syndrome of heart failure resulting from impaired pump function assessed by measuring left ventricular (LV) ejection fraction. The syndrome of SHF may be either chronic or acute, but the pathophysiology of its progression is similar.

**Chronic Systolic Heart Failure**

The major risk factors for the development of SHF are diabetes, hypertension, and ischemic heart disease. Over a given 10 yrs, heart failure develops in 10% of men and 18% of women with diabetes, 12% of men and 8% of women with hypertension, and 30% of men and 30% of women following myocardial infarction.

The most common etiology of SHF in Western countries is ischemic heart disease, which accounts for the approximately 70% of patients with this syndrome (ischemic dilated cardiomyopathy). Of the 30% of patients with nonischemic dilated cardiomyopathy, approximately 13% of patients have idiopathic dilated cardiomyopathy.

Pathophysiology. Left ventricular remodeling is the principal mechanism for the progression of heart failure (1). The major functional and morphologic features of remodeling in SHF are summarized in Table 1. An increase in LV end-diastolic and end-systolic volumes with a reduction in the ejection fraction is the most consistent feature. There is altered ventricular shape and geometry, with the LV shape becoming globular (Fig. 1). Left ventricular mass is increased, usually due to eccentric hypertrophy, but the cavity/mass ratio is increased due to a disproportionate increase in the cavity size. The LV wall thickness in general remains unchanged. As a result, LV wall stress is significantly increased, which is a major determinant of reduced ejection fraction. The depressed contractile function also contributes to reduced ejection fraction.

In approximately 30% of patients, there is mechanical dyssynchrony with or without electrical dyssynchrony. Mechanical dyssynchrony refers to an abnormal sequence of contraction and relaxation of the various myocardial segments and is associated with further impairment of pump function and hemodynamics.

In SHF, adverse remodeling is associated with unfavorable prognosis. In patients with acute coronary syndromes, even after successful recanalization of the infarct-related artery, the risk of development of heart failure and mortality increases with increasing end-diastolic and end-systolic volumes and is inversely related to the ejection fraction.

The precise mechanisms for initiation and progression of remodeling remain unclear. However, neurohormonal activation and a substantial impairment of systolic function appear to be necessary precursors. Neurohormonal activation occurs early in patients with reduced ejection fraction even before the symptoms of overt failure develop. Adrenergic, renin-angiotensin-aldosterone systems, and vasopressin are activated in patients with asymptomatic LV systolic dysfunction. In patients with overt heart failure, the neurohormonal activations are more severe (2).

The activation of renin-angiotensin, aldosterone, and adrenergic systems is associated with myocyte hypertrophy, myocyte apoptosis and necrosis, fibroblast growth, and increased fibrosis. There is also increased oxidative stress, which can produce cytotoxicity.

Neurohormonal activation can promote atherothrombotic and inflammatory responses. There is also vascular remodeling associated with smooth muscle cell hypertrophy. Neurohormonal activation is also associated with increases in systemic vascular resistance, ventricular filling pressures, and arterial stiffness, which may produce adverse effects on cardiac performance. The adverse effects of neurohormonal activation are summarized in Table 2.

Therapy. Initial therapy consists of neurohormonal modulation with pharmacologic agents that have been proven to produce reverse remodeling, alleviate symptoms, improve quality of life, and improve prognosis (3). Renin-angiotensin system inhibition using either angiotensin converting enzyme inhibitors or angiotensin receptor subtype I receptor...
blocking agents has been shown to improve prognosis substantially, as has adrenergic system blockade with the use of oral β-blockers. In patients with symptomatic heart failure despite angiotensin and adrenergic attenuation therapy, aldosterone antagonists improve clinical status and prognosis. The combination of oral hydralazine and isosorbide dinitrate, which has nitric oxide-enhancing properties, improves prognosis of patients with systolic heart failure, particularly African Americans, irrespective of background initial therapy.

In patients who remain symptomatic, diuretics may be necessary to relieve congestion, but diuretic therapy alone is associated with adverse neurohormonal activation and hemodynamic effects, including decreased cardiac output and increased systemic vascular resistance. Similarly, digoxin can be used to improve symptoms, although such therapy has the potential to increase arrhythmic deaths. However, with a digoxin blood level <1.0 μg/mL, this complication is rare and digoxin therapy may decrease morbidity, such as hospital admission rates for treatment of congestive heart failure. The initial therapy in SHF is summarized in Table 3.

In advanced symptomatic SHF, nonpharmacologic therapy may be necessary. Chronic resynchronization treatment with or without an implantable defibrillator should be considered (4). In refractory heart failure, cardiac transplantation may be required. Revascularization and mitral valve repair may be of benefit in selected patients. Enhanced external counterpulsation, implantable ventricular assist devices as destination therapy, and stem cell therapy remain experimental. The nonpharmacologic treatments for advanced SHF are summarized in Table 4.

Acutely Decompensated Heart Failure. Decompensation in a patient with heart failure, due to either acute exacerbation or progressively worsening heart failure, is associated with poor prognosis (5). This is the most common hospital discharge diagnosis for patients >65 yrs old, comprising about 1 million hospital admissions and approximately 6.5 million hospital days per year. The rate of hospital admissions has increased during the last 2 decades, increasing by 90% in the last 10 yrs, and hospital readmissions are also frequent; approximately 20% of patients are readmitted within 30 days and 50% within 6 months.

The mortality rate of patients with acutely decompensated heart failure is high; mortality at 30 days, 12 months, and 5 yrs is 12%, 33%, and 50%, respectively. A number of factors may precipitate decompensation in patients with chronic heart failure. Atrial fibrillation, silent or manifest ischemic episodes, worsening renal function, anemia, and pulmonary embolism may cause exacerbation of heart failure.

The diagnosis of decompensated heart failure is often difficult. The majority of patients present with dyspnea, but dyspnea may be caused by noncardiac causes. Chest radiograph should be obtained but may not always show overt signs of pulmonary venous congestion. Measurement of B-type natriuretic peptide (BNP) or N-terminal proBNP can be useful to distinguish between cardiac and noncardiac dyspnea, as a normal level suggests noncardiac dyspnea.

Management. Patients with decompensated heart failure usually require hospitalization. Supplemental oxygen to restore and maintain adequate oxygenation in patients presenting with hypoxia is particularly important; if necessary, endotracheal intubation should be considered early.

If there is evidence of intravascular (usually venous) and extravascular volume overload with elevated systemic venous pressures, aggressive diuretic therapy is required. Intravenous loop diuretics are used initially; sometimes combinations of diuretics (loop diuretics, thiazide diuretics, aldosterone antago-

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Table 1. Systolic heart failure—remodeling

<table>
<thead>
<tr>
<th>Usually eccentric hypertrophy</th>
<th>Disproportionate increase in ventricular cavity size</th>
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<tr>
<td>Increased ventricular mass</td>
<td>Increased wall stress</td>
</tr>
<tr>
<td>Cavity mass ratio increased</td>
<td>Reduced ejection fraction</td>
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<tr>
<td>Wall thickness—decreased or unchanged</td>
<td>Altered ventricular shape and geometry</td>
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<td>Frequent mechanical dysynchrony with or without electrical dyssynchrony</td>
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Table 2. Adverse effects of neurohormones

| Myocyte hypertrophy | Vascular smooth muscle cell hypertrophy | Fibroblast growth | Promotion of programmed cell death (apoptosis) | Promotion of atherothrombosis | Stimulation of proinflammatory modulators | Ventricular and vascular remodeling | Abnormal central and peripheral hemodynamics |

Table 3. Systolic heart failure—initial therapy

| Angiotensin-converting enzyme inhibitors (ACEIs) | Angiotensin receptor-blocking agents if ACEIs are not tolerated | β-blocking agents | Aldosterone antagonists | Hydralazine-isosorbide dinitrate in African Americans | Digitalis in selected patients | Diuretics for congestive symptoms |

Table 4. Nonpharmacologic interventions

| Chronic resynchronization therapy with or without implantable cardioverter defibrillator | Cardiac transplantation | Revascularization | Left ventricular volume reduction surgery | Batista, Dore, Saver procedures | Mitral valve repairs | Dual-chamber pacemaker pacing with short P-R interval | Ventricular assist devices | Passive ventricular constraint devices | Myosplints | Mesh jacket |

Figure 1. A magnetic resonance image of a patient with ischemic systolic heart failure, illustrating a dilated globular heart with no increases in left ventricular thickness.
nists, and rarely carbonic anhydrase inhibitors) are required.

In patients with volume overload refractory to diuretics, ultrafiltration or dialysis should be considered. In patients with evidence of impaired organ perfusion (e.g., worsening renal function) with or without hypotension, vasoactive drug therapy should be considered. In the presence of hypotension, drugs that can maintain arterial pressure by increasing systemic vascular resistance, such as noradrenaline or phenylephrine and dopamine, are often necessary. To maintain adequate cardiac output, intravenous positive inotropic drugs (β-adrenergic agonists, phosphodiesterase inhibitors, or calcium sensitizing agents) are frequently used. In some patients hospitalized for decompensation, intravenous exogenous BNP can improve hemodynamics and symptoms. In patients refractory to pharmacotherapy, ventricular assist devices can be considered as a bridge to transplant therapy. In very select patients, implantable assist devices are employed as destination therapy, but the prognosis of these patients remains very poor. Newer and more sophisticated assist devices are being developed for long-term treatment of patients with refractory heart failure.

Hemodynamic stabilization in patients with ischemic or nonischemic cardiomyopathy takes precedence, and intraaortic balloon counterpulsation may be useful in this respect. Until a patient is stabilized, resynchronization treatment with or without implantable cardioverter and defibrillators is not appropriate. Similarly, revascularization should not be considered in very unstable patients. The therapies for decompensated heart failure are outlined in Table 5.

### Acute Heart Failure in Newly Diagnosed Cardiomyopathy

Whereas making the diagnosis of heart failure in a patient with classic signs and symptoms may be straightforward, the management of a patient with a new presentation of cardiomyopathy—including the decision whether to pursue endomyocardial biopsy to define the etiological process—may be one of the most difficult clinical challenges in the care of the patient with cardiovascular disease. The importance of adequate and timely intervention—especially when the need arises for inotropic or mechanical support—cannot be overstated in this patient population. The variable spectrum of clinical presentations ranges from asymptomatic pulmonary venous congestion to cardiogenic shock. Despite the complexity behind the clinical decision making that can challenge even the most adept clinician, relatively few guidelines exist to aid in the care of the newly diagnosed cardiomyopathy patient in heart failure. The aim of this section is to address the evaluation, initial management, need for mechanical support, and consideration for orthotopic heart transplantation of the patient presenting with acute heart failure in the setting of newly diagnosed nonischemic cardiomyopathy. The first task, however, will be to refine further the characteristics of this patient population, clarifying how such patients differ from the clinical profile of acute decompensation of chronic heart failure.

#### Patient Population

The patient of interest will often be referred for further workup of new-onset cardiomyopathy after it has been established, by either coronary angiography or history and risk factor profiling, that the likelihood that either flow-limiting coronary disease or prior myocardial infarction with extensive remodeling can explain the degree of ventricular dysfunction is very low. Patients with an acute cardiomyopathy can present with highly variable clinical scenarios, including chest pain, effort intolerance due to dyspnea or fatigue, systemic edema, dynamic change in LV systolic function, syncope due to tachyarrhythmias or heart block, or cardiogenic shock. The most concerning feature common to patients with an acute nonischemic cardiomyopathic process is a decline in LV systolic function that is often but not invariably associated with worsening congestive heart failure. The clinical manifestation of this decline in ventricular performance will often be symptomatic left, right, or biventricular failure, but relatively asymptomatic presentations can occur, and a high index of suspicion is required for a progressive cardiomyopathic process in this setting.

Electrocardiographic manifestations include changes in rhythm, such as complete or partial loss of atrioventricular conduction, and altered ventricular depolarization, with the development of left or right bundle branch block or prolongation of the QT interval.

A decline in clinical status, such as worsening heart failure or increased frequency of ventricular arrhythmias, may not parallel the decline in ventricular function. This is why a high index of suspicion for a progressive cardiomyopathic process with an appropriate threshold for endomyocardial biopsy has to be maintained during the evaluation of a patient with unexplained new-onset LV systolic dysfunction.

#### History and Physical Examination

The key aspect of the history in the evaluation of this patient is securing the time course of the illness. The effort tolerance, stamina, level of fatigue, and weight of the patient with acute cardiomyopathy can change over a short period of time, but this is not true in all cases—cardiovascular performance can be maintained with absent cardiac symptomatology in cases presenting with fever and electrocardiographic abnormalities accompanying severe LV systolic dysfunction. When right heart failure is present predominantly or concomitantly with left heart failure, abdominal complaints such as distention, right upper quadrant or nonfocal abdominal pain, and nausea may be elicited. The level of decompensation varies significantly, with some patients often noting some modest change in their routine level of activity or exercise and others presenting with more severe signs and symptoms of heart failure such as dyspnea at rest, orthopnea, or lower extremity swelling. The clinical presentation of acute lymphocytic myocarditis is often similar to that of a patient with newly diagnosed heart failure in the setting of chronic idiopathic dilated cardiomyopathy. Subacute or even acute onset of symptoms does not imply the presence of an acute cardiomyopathic/acute myocarditis syndrome—new-onset heart failure in the setting of long-standing LV systolic dysfunction very often presents in such manner.

Besides congestive heart failure, which is most common in the presence of an acute cardiomyopathy with LV dysfunction, other symptoms that may be elicited include chest pain, often with a pleuritic component, fever, and palpitations. Chest pain was present in one fifth to one third of patients in the Interven-
tion in Myocarditis and Acute Dilated Cardiomyopathy (IMAC) study (7) and the Myocarditis Treatment Trial (MTT) (8), which studied the efficacy of immunosuppression in acute myocarditis. Chest pain may be associated with pericardial inflammation in patients with myocarditis or it may be the only manifestation of heart failure in a subset of patients. Although the etiology of acute myocarditis is often viral, cardiac involvement often occurs without any systemic signs of viral illness. Fever was present in only 19% of patients in the MTT (8), and up to one third of patients with acute myocarditis from a single-center registry had no fever or other symptoms of a viral prodrome (9). This is consistent with the reported prevalence of an antecedent viral syndrome of about 60% in patients randomized in the MTT and in the IMAC study. Palpitations may be the only presenting symptom in acute cardiomyopathy, being the manifestation of atrial or ventricular dysrhythmias, such as atrioventricular block and ventricular tachycardia. As with heart failure symptoms, the time course is an essential component to elicit, as recent onset and more frequent palpitations or recurrent syncope may be the only symptom complex in a young patient with an acute progressive cardiomyopathy. After a symptom complex has been elicited, a complete family history should be taken to determine whether the presence of heart failure, dilated cardiomyopathy, or sudden death in a close relative of the patient is suggestive of a familial dilated cardiomyopathy.

An important subset of patients with acute myocarditis who manifest a more severe presentation is the group with recent-onset cardiomyopathy with fulminant myocarditis. On the basis of clinico-pathologic criteria, Lieberman and others (10) classified acute lymphocytic myocarditis as either fulminant or nonfulminant. Patients with acute fulminant myocarditis are more likely to be critically ill at the time of presentation and have a more intense inflammatory infiltrate on endomyocardial biopsy but paradoxically were found to have a better outcome, often with recovery of ventricular function (11). In the single-center registry-based study at the Johns Hopkins Hospital, 147 patients diagnosed with acute lymphocytic myocarditis had no other disease process known to be associated with myocardial inflammation. Fifteen of the 147 (10%) had fulminant myocarditis—two requiring circulatory assistance with mechanical support and the remainder on high-dose inotropic and vasopressor therapy. During an average follow-up of 5.6 yrs, only one of 15 patients with fulminant myocarditis died and none required orthotopic heart transplantation. In contrast, the 5-yr transplantation-free survival in patients with acute (nonfulminant) myocarditis was 70%, and only 48% of these patients were alive without having undergone cardiac transplantation at 11 yrs (11).

Another subset of patients with a nonischemic cardiomyopathy presenting with acute heart failure that almost invariably resolves have the syndrome of LV systolic dysfunction associated with emotional stress (12) or neurocardiogenic stunning due to intracerebral or subarachnoid hemorrhage (13). The echocardiogram often demonstrates LV dysfunction with a pattern of apical ballooning and sparing of LV function at the base. Eliciting a precise history including time course of symptoms, events associated with severe emotional stress, and neurogenic events such as headache is essential in making the diagnosis of this acute cardiomyopathy that may require transient support of LV function with a high likelihood of complete recovery within weeks of presentation (12).

The physical examination in acute cardiomyopathy syndromes should be directed to make an accurate hemodynamic assessment of the patient at the time of presentation and to not overlook physical signs, such as rash and lymphadenopathy, associated with a viral or other infectious prodrome in acute myocarditis. Tachycardia was more common at the time of presentation in patients with acute fulminant myocarditis, compared with patients who had acute nonfulminant myocarditis, who also presented with a higher mean arterial pressure (11). Despite elevation of left-sided filling pressures, rales may be absent not unlike the pulmonary examination in acute decompensation of chronic heart failure. Evidence for the elevation of right-sided filling pressures, such as elevated jugular venous pressure, the presence of a positive abdominojugular reflex, hepatomegaly and right upper quadrant tenderness, and peripheral edema, may indicate right ventricular (RV) involvement since the concordance of right- and left-sided filling pressures usually present in chronic heart failure (14) may not be as high in the group of patients with acute heart failure. The presence of a left, right, or biventricular third heart sound implicates hemodynamic decompensation, but the adverse prognostic significance of a third heart sound or an elevated jugular venous pressure shown in patients with chronic systolic heart failure (15) has not been investigated in this group with acute cardiomyopathy syndromes. As in the case of decompensated acute on chronic heart failure, the peripheral examination— including the pulse and pulse pressure—may indicate a low-output state if the extremities are cool, the pulse intensity is variable, or the pulse pressure is narrow.

Electrocardiography and Imaging. Despite the availability of echocardiography and cardiac magnetic resonance imaging (MRI), the electrocardiogram should not be overlooked in the evaluation of patients with acute cardiomyopathy. Commonly, nonspecific ST and T wave abnormalities are present (16). The presence of PR depression and diffuse ST elevation in the appropriate clinical scenario of acute fever and chest pain secures the diagnosis of pericarditis in a patient who may have a concomitant inflammatory cardiomyopathy. Although uncommon, Q waves with ST segment abnormalities may be indistinguishable from electrocardiographic changes of myocardial infarction—in such cases prompt coronary angiography should exclude the presence of an acute ischemic event, and a negative study raises the possibility of myocarditis mimicking acute myocardial infarction (17, 18). Ventricular arrhythmias such as monomorphic ventricular tachycardia, fascicular or complete left bundle branch block, and atrioventricular block are common and important signs, especially when there is electrocardiographic progression as seen in patients with idiopathic giant-cell myocarditis (19) or acute myocarditis (20).

Echocardiography at the time of presentation should be performed to assess RV and LV size and function as well as secure a baseline for comparison with future echocardiographic examinations that may signify disease progression. The presence of a small or normal ventricular cavity size, decreased systolic function, pericardial effusion, and increased LV wall thickness should be highly suggestive of active myocardial inflammation. Although global depression of LV systolic function is one presentation, there can also be regional wall motion abnormalities with acute myocarditis as with the
acute cardiomyopathic process. The more patient with signs and symptoms of an shows preserved LV systolic function in a initial echocardiographic observation RV and LV dysfunction and geometry The superiority of cardiac MRI in defining imaging of inflammatory myocardium. promising development in noninvasive monly observed (12, 13).

stress or neurocardiogenic stunning. In a study using echocardiography showed that the degree of LV systolic function at baseline did not distinguish patients with acute fulminant from those with nonfulminant myocarditis (21), but patients with fulminant myocarditis had significantly less ventricular dilation at baseline (LV end-diastolic diameter 5.3 ± 0.9 cm vs. 6.1 ± 0.8 cm) but greater septal thickness (1.2 ± 0.2 cm vs. 1.0 ± 0.1) than acute nonfulminant myocarditis. At 6 months, the patients with fulminant myocarditis showed a marked improvement in fractional shortening, whereas patients with acute nonfulminant myocarditis did not. Echocardiographic findings can also be used to distinguish the cardiomyopathy of apical ballooning related to acute stress or neurocardiogenic stunning. In this case, varying degrees of anteroseptal and classically apical dyskinesis with LV function intact at the base are commonly observed (12, 13).

The emerging role of cardiac MRI is a promising development in noninvasive imaging of inflammatory myocardium. The superiority of cardiac MRI in defining RV and LV dysfunction and geometry should be considered in cases where the initial echocardiographic observation shows preserved LV systolic function in a patient with signs and symptoms of an acute cardiomyopathic process. The more precise definition of RV function that can be achieved with cardiac MRI may be able to risk stratify patients with acute myocarditis, as recent studies have demonstrated that decreased RV systolic function is associated with an increased risk of death or cardiac transplantation (22). Furthermore, cardiac magnetic resonance with delayed enhancement imaging is sensitive in detecting areas of myocardial inflammation, often demonstrating the segmental involvement (Fig. 2) in active myocarditis that may underlie the limited sensitivity of endomyocardial biopsy (23, 24). In cases of acute cardiomyopathy with apical ballooning, contrast MRI with delayed gadolinium is expected to be negative for hyperenhancement since LV dysfunction is due to neurocardiogenic myocardial stunning (25). In a progressive process of myocardial inflammation with myocardial necrosis, such as idiopathic giant-cell myocarditis or severe lymphocytic myocarditis, one would expect to see areas of hyperenhancement with delayed-perfusion cardiac MRI—often in a segmental pattern but not subendocardial as would be expected in myocardial infarction (26).

Invasive Hemodynamic Assessment. A formal hemodynamic assessment should be at least considered in all patients with acute heart failure and new-onset cardiomyopathy. An accurate determination of filling pressures and cardiac output after initial diuresis-natriuresis may determine the need for inotropic or mechanical support in a patient with progressive myocardial inflammation and systolic dysfunction. Hemodynamic subsets that are characteristic of a specific disease process underlying acute cardiomyopathy do not exist. In the single-center registry-based study at the Johns Hopkins Hospital, the mean pulmonary artery occlusion pressure, mean pulmonary arterial pressure, and cardiac output were similar in patients with acute fulminant and nonfulminant myocarditis (11). Another single-center registry-based study at the same institution identified elevated pulmonary artery pressure and pulmonary vascular resistance as independent predictors of mortality in 1,134 patients with newly diagnosed cardiomyopathy (27). Furthermore, this study found a significant interaction between high pulmonary artery pressures and endomyocardial biopsy-proven myocarditis on mortality so that the relative risk of death associated with secondary pulmonary hypertension was higher in the group of patients with new cardiomyopathy who had acute myocarditis.

Etiology and Role of Endomyocardial Biopsy. The etiology of a newly diagnosed nonischemic cardiomyopathy can be subdivided into 1) inflammatory causes; 2) cardiotoxicity; 3) metabolic-nutritional and endocrine abnormalities; 4) familial dilated cardiopathies; 5) nonischemic myocardial stunning; and 6) tachycardia-mediated cardiomyopathies. The most critical characterization, one that must be determined as early as possible in the course of illness, is whether the cardiomyopathic process is progressive or stable (Fig. 3). Worsening LV or RV systolic function or progressive myocardial remodeling with ventricular dilation could signal an aggressive inflammatory process of myocardium—such as fulminant or idiopathic giant-cell myocarditis. Alternatively, a progressive cardiomyopathic process may be due to the acute effects of a cardiotoxic agent, such as interferon-α—a cardiomyopathy that is known to resolve with discontinuation of the drug (28). In deciding whether to pursue endomyocardial biopsy, the clinician should keep in mind that the clinical course does not often parallel progression or regression of the cardiomyopathic process. Heart failure or arrhythmias that are stable—especially on aggressive diuretic/vasodilator or antiarrhythmic therapy—may not reflect the deterioration in ventricular function.
that can take place in an undiagnosed case of idiopathic giant-cell myocarditis. As in the case of a formal hemodynamic assessment, an endomyocardial biopsy should at least be considered in every case of acute heart failure due to newly diagnosed cardiomyopathy. Although controversy exists regarding the indication of endomyocardial biopsy in this patient population, we believe that a pathologic assessment of the myocardium is essential in the following clinical scenarios: 1) distinguishing acute (fulminant or nonfulminant) myocarditis from idiopathic giant-cell myocarditis (Fig. 4) in a patient with nonischemic cardiomyopathy with clinical features suggestive of a rapidly progressive cardiomyopathic process; 2) diagnosing myocardial sarcoidosis—either acute fulminant myocardial sarcoidosis or chronic active sarcoid—in the appropriate clinical setting; 3) diagnosing anthracycline cardiotoxicity in a patient with declining LV systolic function who has not completed anthracycline-based chemotherapy or who is demonstrating an initial response to this regimen; and 4) defining the etiology of a restrictive cardiomyopathic process with or without LV systolic dysfunction. A strategy of aggressive immunosuppression can be initiated if a diagnosis of idiopathic giant-cell myocarditis or active myocardial sarcoidosis is made early in the disease process.

Initial Management. As with the patient in acute decompensation of chronic heart failure, the initial therapy is targeted to get the patient out of heart failure. If the physical examination or invasive hemodynamic assessment has established elevated filling pressures, intravenous diuretic or other volume-optimizing therapies (natriuretic or aquaretic) should be initiated. If the initial assessment is consistent with a low-output hypervolemic state—"cold and wet"—inotropic or intravenous vasodilator therapy should be initiated, depending on the adequacy of systemic pressure. The most important management tool in the patient with acute new-onset cardiomyopathy with severe heart failure is continuing assessment of the hemodynamic response to therapy and vigilance for signs of a rapidly progressive cardiomyopathy, including development of arrhythmias. Has there been sufficient diuresis after intravenous furosemide? Has the heart rate stabilized with improved mean arterial pressure after the initiation of low-dose dobutamine? Improvement in markers of neurohormonal activation—such as BNP—can also be used as indicators of an appropriate response to initial therapy. However, the majority of studies correlating the neurohormonal and hemodynamic responses to therapy were done in patients with acute decompensation of chronic heart failure without an active myocardial disease process such as acute myocarditis. If there is severe and ongoing myocardial necrosis, activation of the natriuretic peptide system may lead to very high serum levels of A-type natriuretic peptide or BNP that may not correlate with the degree of hemodynamic compromise but are related to the degree of neurohormonal activation. Although worsening renal function has been validated as an important prognostic indicator in patients with decompressed heart failure, the prognostic role of baseline or worsening renal function has not been confirmed in patients with acute myocarditis. Nevertheless, clinical assessment of renal and hepatic function remains important in evaluation of the initial response to therapy and the progression or stabilization of the cardiomyopathic process.

The recommended medical therapy for acute myocarditis with LV systolic dysfunction is similar to the neurohormonal blockade that is initiated in patients with symptomatic LV dysfunction due to chronic dilated cardiomyopathy. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers and β-adrenergic antagonists are recommended for all patients, as well as consideration (especially in New York Heart...
Association class III or IV patients) of aldosterone blockade. The current expectation with optimal medical therapy for acute (nonfulminant) myocarditis is that 30% to 50% of patients will achieve significant recovery of LV systolic function, with the majority of the remaining patients developing chronic dilated cardiomyopathy and a small proportion demonstrating a progressive heart failure course requiring advanced therapies, such as cardiopulmonary bypass or mechanical support with or without bridging mechanical support of a ventricular assist device.

Immunosuppression. The role of immunosuppression in the progression of acute myocarditis to dilated cardiomyopathy has been the basis of intense clinical interest over the last 10–15 yrs. The hypothesis that an early strategy of immunosuppression would be beneficial in curtailing progression to dilated cardiomyopathy in patients with acute myocarditis has been seriously challenged by prospective randomized trials of immunosuppression or immune modulation that have failed to identify any significant treatment effect in this population (7, 8, 29). Furthermore, in both the MTT and the IMAC study, patients with higher systemic markers of active inflammation—higher baseline tumor necrosis factor-α levels in IMAC and higher white blood cell or autoantibody titer in the MTT—tended to have less initial impairment of ventricular function and more LV recovery. Currently, the large multicenter European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) is combining histologic and genetic techniques to identify patient subsets for therapeutic strategies, including antiviral and immunosuppressive therapies that are tailored to the specific immune response and the detection of viral genomes of the patient with acute myocarditis (30).

The early diagnosis of idiopathic giant-cell myocarditis is becoming increasingly relevant, as evidence from case series and the Giant Cell Registry supports a therapeutic benefit for a strategy of early aggressive immunosuppression in this patient population, especially the combination of cyclosporine and the anti-T-lymphocyte antibody muromonab-CD3 (19, 31). The Giant-Cell Myocarditis Study Group included 63 patients from 49 medical centers in 16 countries with a histologically proven diagnosis of idiopathic giant-cell myocarditis. The rate of death or cardiac transplantation was 89% with a median transplant-free survival of 5.5 months from the onset of symptoms. Cumulative mortality from all causes was greater in this cohort compared with the 111 patients with lymphocytic myocarditis participating in the MTT (p < .001). The 22 patients who received combined immunosuppressive therapy (various combinations of steroids plus OKT3 or cyclosporine or azathioprine) had a longer transplant-free survival than those who received no immunosuppression (12.3 months vs. 3.0 months, p < .001). The sensitivity of endomyocardial biopsy for diagnosing giant-cell myocarditis was estimated at about 80% from this Multicenter Giant Cell Myocarditis Registry (19). Given the markedly different strategy of early aggressive immunosuppression that may be taken, we recommend that all patients with new cardiomyopathy presenting with severe heart failure undergo endomyocardial biopsy with sufficient quality sampling to confirm or exclude the presence of giant-cell myocarditis. A prospective randomized controlled trial is currently enrolling patients with idiopathic giant-cell myocarditis who have not required mechanical support in order to estimate the treatment effect of various strategies of early immunosuppression.

Mechanical Support and Cardiac Transplantation. As in the management of acute decompensated heart failure in the setting of chronic cardiomyopathy, mechanical circulatory support should be considered in patients who remain in heart failure and demonstrate signs of end-organ hypoperfusion despite optimal management with intravenous inotropic and vasodilator agents. Patients with fulminant myocarditis, who by definition have acute worsening LV dysfunction with significant hemodynamic compromise, have been shown to have a good long-term prognosis, often with normalization of LV ejection fraction, if adequate mechanical support with ventricular assist device (32, 33) or extracorporeal membrane oxygenation (34) can bridge them to recovery during the acute fulminant phase. In this fulminant subgroup, along with patients diagnosed with idiopathic giant-cell myocarditis who are candidates for cardiac transplantation, it is important to recognize the need for mechanical circulatory support early and before the manifestation of moderate or severe end-organ damage.

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REFERENCES


