Cardiol

THE DILATED CARDIOMYOPATHIES AND RELATED SYNDROMES

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A cardiomyopathy is a diffuse or multifocal disease of the myocardium not due to cardiovascular disease extrinsic to the myocardium. Disease such as the high output states, valvular, pericardial, congenital or coronary artery diseases are excluded. Some cardiomyopathies are secondary to known diseases elsewhere in the body (e.g., hemochromatosis). Cardiomyopathies may be classified according to the hemodynamic disorder: dilated, obstructive, and restrictive-obliterative (Table 1). These simple catagories are valuable because the etiologies, clinical findings and management of the three types of myopathies are quite different (99,100,122-24,198,258).

The first symptoms of heart failure do not permit the physician to differentiate among these classes. The restrictive-obliterative cardiomyopathies (amyloid, endomyocardial disease, neoplastic infiltration, ventricular thrombosis, etc.) may present with symptoms of severe heart failure, although cardiac enlargement is usually minimal. Similarly, patients with hypertrophic myopathies may develop symptoms of failure, but the physical exam is usually distinctive and heart enlargement is also minimal.

A patient with a dilated cardiomyopathy should be carefully evaluated since this is the only cardiomyopathy which is occasionally reversible. The dilated cardiomyopathies which should be considered in the United States will be reviewed. Cardiac manifestations of systemic diseases will not be mentioned unless a patient may present with cardiac findings. Very rare causes of dilated cardiomyopathy, particularly infections and hypersensitivity reactions, are reviewed elsewhere (122-24,184,258).

Table 1. Hemodynamic classification of the cardiomyopathies. LVEF, left ventricular ejection fraction.

Class	LVEF	LV chamber volume	Mechanism of failure	Typical therapy
Restrictive-Obliterative	0.4-0.7	nl	diastolic	symptomatic
Hypertrophic	0.5-0.9	nl	diastolic	- inotrope
Dilated	< 0.4		systolic	+ inotrope diuretic vasodilator

The diagnosis of cardiomyopathy usually requires normal epicardial coronary arteries. However, the phrase "ischemic cardiomyopathy" has been coined and deserves mention since it is probably the most common cause of the clinical findings of dilated cardiomyopathy in the United States (124).

The prevalence of dilated cardiomyopathy is about 1/10,000 population which is about twice that of primary hypertrophic cardiomyopathy and more common than restrictive / obliterative cardiomyopathy (253). A dilated cardiomyopathy should be considered if a patient presents with fatigue and dyspnea, if heart failure is discovered incidentally, or if a patient reports heart failure that spontaneously improves.

TYPICAL PATHOLOGY OF DILATED CARDIOMYOPATHY

The pathological findings of three important dilated cardiomyopathies (alcohol related, peripartum and idiopathic) are identical (6,13,14,34,99,122-124,169,170). Grossly, the left ventricle and sometimes all four chambers are dilated. Heart mass is increased, and the ventricular walls are mildly thickened, roughly in proportion to chamber volume. The valves are normal, although there may be slight dilation of the mitral valve annulus. The myocardium is pale. Endocardial scarring may occur. Mural thrombi in any of the chambers are common. The coronary arteries are normal.

Light microscopic studies show interstitial fibrosis and mild perivascular fibrosis, but replacement fibrosis is not common. Small areas of necrosis and infiltrates may be seen, but these are not prominent. Cellular hypertrophy is invariably evident. Increased numbers of lipid droplets may be seen. Electron microscopic studies show sarcoplasmic reticular abnormalities, swelling of the mitochondria, increased glycogen granules and myofibrillar lysis. The number of neurons may be decreased. Enzyme defects have been described, but these may simply be secondary to heart failure. Reduced levels of mitochondrial enzymes with increased lactate dehydrogenase could represent an adaptation to enhanced anaerobic glycolysis. None of these findings provide a specific diagnosis.

PATHOPHYSIOLOGY OF CONGESTIVE FAILURE DUE TO SYSTOLIC MYOCARDIAL FAILURE

The gradual impairment of systolic performance triggers a cascade of events which generate clinical congestive heart failure and may also aggravate the myocardial disease. A distinction is made between myocardial failure which indicates reduced systolic performance, and congestive failure which implies volume overload and sodium retention. Severe myocardial failure may be present with normal left ventricular filling pressures without obvious sodium retention. Therefore, venous congestion is not always observed in these patients, especially early in the disease or after aggressive diuretic therapy.

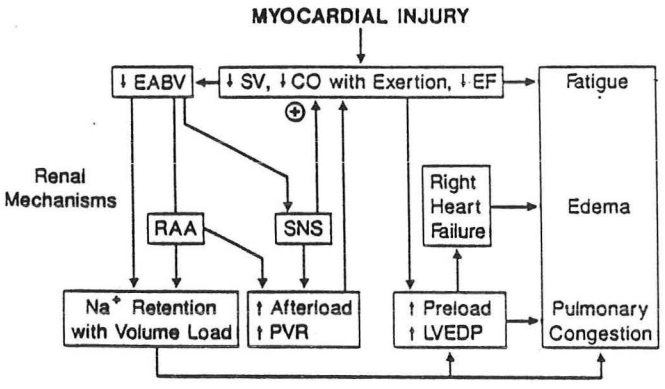


Figure 1. Overview of the pathophysiology of left ventricular failure. CO, cardiac output; EABV, effective arterial blood volume; EF, ejection fraction; LVEDP, left ventricular end diastolic pressure; RAA, renin-aldosterone-angiotensin system; PVR, peripheral vascular resistance; SNS, sympathetic nervous system; SV, stroke volume.

Progressive deterioration of patients with dilated cardiomyopathies occurs in three steps: repeated tissue injury, stimulation of compensatory mechanisms, and progressive functional deterioration which may in part be promoted by the early compensatory responses.

The fundamental defect of the dilated cardiomyopathies is impaired systolic contractile function which leads to the characteristic clinical feature: left ventricular ejection fraction less than 0.40 (ejection fraction is defined as stroke volume/end diastolic volume). Contractile failure leads to three compensatory mechanisms which tend to preserve myocardial performance: increased left ventricular volumes, myocardial hypertrophy, and increased sympathetic drive. In addition, the renin-angiotensin system is activated (25,28,41). The recent description of atrial naturetic factor has added a new dimension to the pathophysiology of failure since its release is provoked by increases in central blood volume. It is an effective naturetic agent and vasodilator. Its high concentration in the blood of patients with heart failure may have beneficial effects (preload reduction due to Na excretion and afterload reduction due to vasodilating properties).

Diastolic pressure load due to left ventricular failure

Impaired left ventricular systolic performance leads to dilation of the heart because of reduced stroke volume. As the left ventricle enlarges the Starling mechanism (increased sarcomere length causes increased contractile force) tends to increase the stroke volume and cardiac output toward the normal range. The increased left ventricular end diastolic volume also results in increased end diastolic pressure (LVEDP), which in turn produces increased left atrial pressure. Although this mechanism is effective at low and intermediate left ventricular pressures, at high end diastolic pressures the stroke volume response to further increases is nearly flat (Figure 2). Thus, pulmonary congestion may progressively worsen as left atrial pressures increase without an associated increase in cardiac output. This also implies that substantial relief of symptoms is possible without compromising cardiac output if ventricular volumes can be reduced.

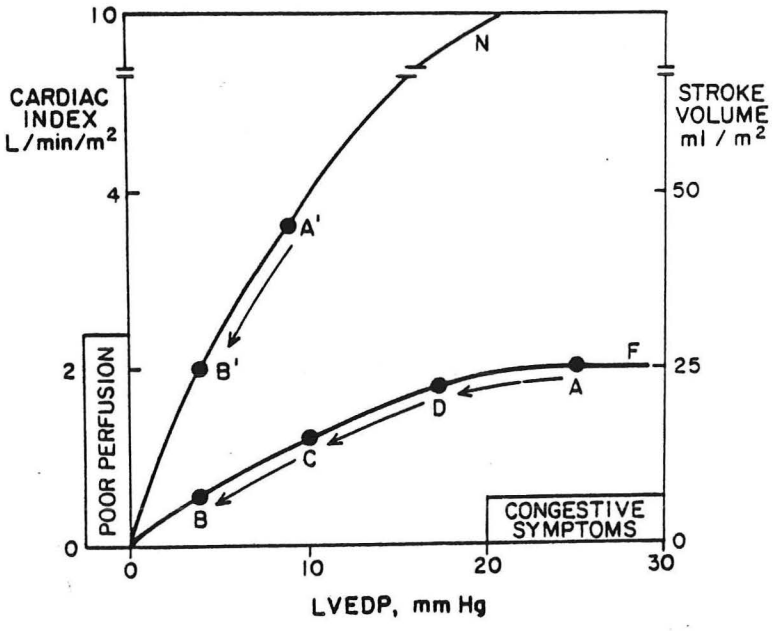


Figure 2. Relationship between systolic performance and LVEDP in congestive heart failure compared to normal myocardium. The normal individual with an LVEDP of 10 mm Hg will suffer decreased cardiac output if EDP decreases (A' to B'). The patient with heart failure (EDP = 25 mm Hg, point A) does not experience a decrease in cardiac output with a moderate decrease in EDP to 18 mm Hg (point D). Dyspnea, however, has improved because of reduced pulmonary venous pressure. (from ref.225)

It should be noted that in dilated cardiomyopathies the LV pressure volume relationship may be "supernormal," that is, for a give volume the diastolic pressure is lower than would be expected in a normal heart (64,70,185). Thus, the LVEDP may be minimally elevated with extreme increases in LV volumes and depression of ejection fraction.

Preload refers to the length of the sarcomeres in the left ventricle during diastole. In clinical terms, this translates to end diastolic volume or end diastolic pressure with normal compliance. As a consequence of increased EDV the cardiac output may be preserved but pulmonary congestion develops. Therefore, therapy must balance reducing end diastolic volume (which improves pulmonary congestion) against a decrease in cardiac output via the Frank-Starling mechanism.

Mild mitral regurgitation is common due to enlargement of the mitral annulus and distortion of the submitral apparatus which is caused by enlargement of the ventricle. Pulmonary hypertension of variable degree is a result of passive transmission of chronically elevated left atrial pressure. Right ventricular enlargement and failure, tricuspid regurgitaion, increased central venous pressure and the complete pictue of right-sided congestive failure may develop without the involvement of the right ventricle by primary disease.

Neurohumoral and renal response to left ventricular failure

These effects of LV failure on the heart are key to interpreting the symptoms, physical findings and hemodynamic data. Effective therapy, however, must address the peripheral circulatory consequences of CHF. From this perspective, the fundamental defect in congestive heart failure is a cardiac output that is not adequate to supply the metabolic demands of the body. This concept is useful since it relates the observed neurohumoral response to the primary heart disease (Figure 1). Reduction in the effective arterial blood volume has 3 consequences: 1) stimulation of the sympathetic nervous system, 2) depression and redistribution of renal blood flow, and 3) activation of the renin - angiotensin -aldosterone (RAA) system.

This activation of the sympathetic nervous system (SNS) increases plasma levels of norepinephrine in patients with CHF. This response is immediately beneficial since it tends to maintain blood pressure and ejection fraction. However, it may be deleterious over prolonged periods. Higher levels of norepinephrine correlate with more severe symptoms, but not with left ventricular function. The relative activity of the SNS and RAA system in an individual is variable. However, high plasma norepinephrine predicts mortality better than high plasma renin in patients with CHF (41).

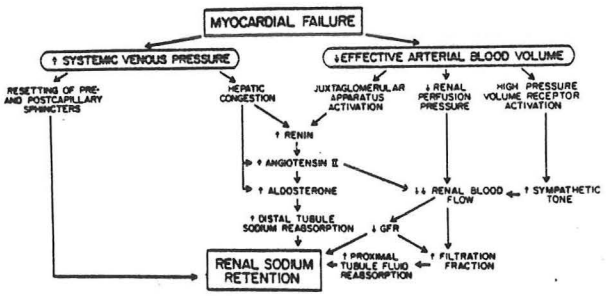


Figure 3. Renal consequences of congestive heart failure. The reduced effective arterial blood volume of CHF provokes a redistribution of renal blood flow and filtration in such a way that sodium is conserved.

The second compensatory mechanism, renal sodium retention, is thought to result from decreased blood volume perceived by intrathoracic volume sensors, possibly the great vessels (214). These sensors regulate, in part, antidiuretic hormone release, the tone or renal arterioles, and renal sympathetic nerve discharge. These factors and a change in relative oncotic and hydraulic pressures, contribute to net sodium and water reabsorption by the kidney (Figure 3).

Activation of the renin - angiotensis - aldosterone system (RAA) is the third compensatory mechanism. Heart failure stimulates the release of renin from the juxtaglomerular cells of the kidney. Renin converts alpha 2 globulin to angiotensin I, and converting enzyme further cleaves the polypeptide to angiotensin II (Figures 4 and 5). This octapeptide has two deleterious effects on the cardiovascular system. It is a powerful vasoconstrictor which increases the systolic load imposed on the left ventricle, and it stimulates the release from the adrenal glands of aldosterone. The resulting sodium retention may have an effect other than simply volume loading: decreased arterial compliance. Patients with CHF may have variable degrees of activation of the RAA system (Figure 6)

Figure 4. Structure of renin substrate (angiotensinogen), angiotensin I and angiotensin II.

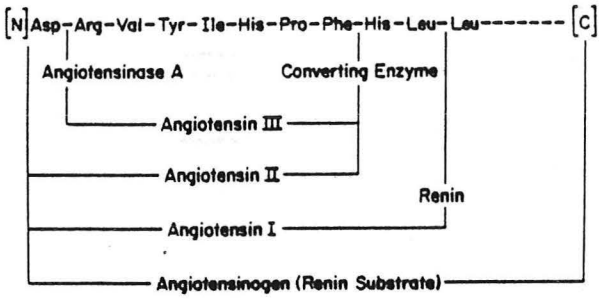
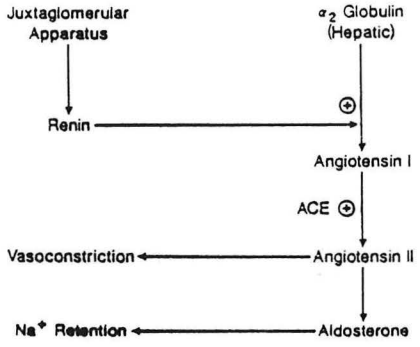


Figure 5. Renin-angiotensin-aldosterone system



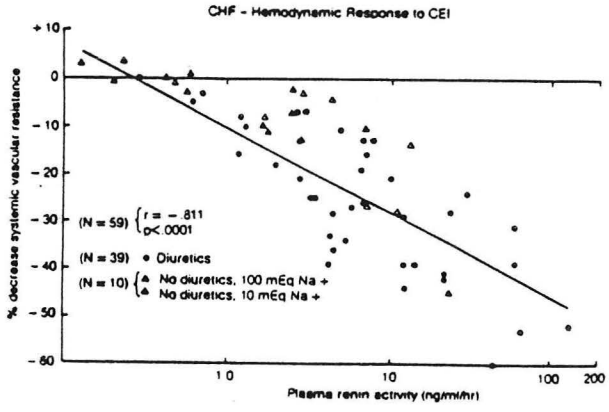


Figure 6. Relationship between plasma renin activity, systemic vascular resistance, and converting enzyme inhibition. Captopril, 25 mg, was given to patients with CHF. At high baseline levels of plasma renin activity there was a marked drop in systemic vascular resistance. When renin was low, however, there was little response, implying that angiotensin II levels are also low.

Aortic impedance and afterload

The ejection of blood during left ventricular systole is in part regulated by afterload. Afterload refers to wall tension in the left ventricle during systole and is approximately proportional to (LV diameter) x (systolic pressure) as described by the LaPlace relationship. Afterload is determined by aortic impedance. This term describes the instantaneous relationship between aortic pressure and flow, and is determined largely by arterial compliance and peripheral resistance. A major component of impedance which is sensitive to drug therapy is systemic vascular resistance (SVR) which is regulated by the arterioles. Although it is incorrect to equate SVR to aortic impedance, patients with severe heart failure generally have marked increases in SVR and the effective vasodilators produce substantial decreases in SVR.

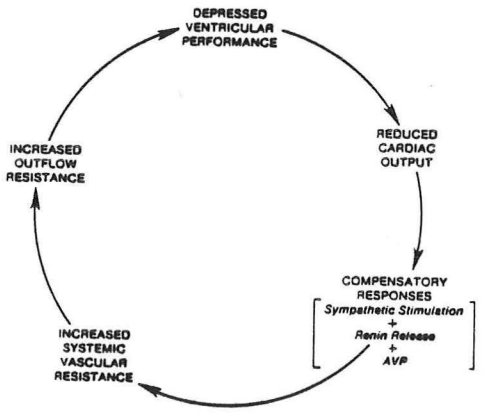


Figure 7. The cycle of myocardial failure and compensatory neurohumoral response. The net effect of neurohumoral activation is to increase aortic impedance.

Myocardial hypertrophy and ischemia

Myocardial hypertrophy is a characteristic feature of most dilated cardiomyopathies. Abnormal loading conditions appear to provoke an increase in muscle mass which is an appropriate response to maintain systolic function. In patients with equivalent degrees of chamber enlargement the presence of hypertrophy is associated with longer survival (22). Coronary vascular reserve and coronary blood flow per unit mass of myocardium are both decreased and may be the mechanism of mild ischemic chest pain in some patients with CHF (181).

2. IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy (IDC), the eminence grise of dilated cardiomyopathies, is less frequent than heart failure due to hypertension and coronary artery disease. The diagnosis of IDC is based on exclusion of alcohol use, recent pregnancy, and the diseases described below. IDC is probably a consequence of diffuse myocardial damage of multiple etiologies. If a specific etiology could be identified then disease-specific therapy could be instituted and asymptomatic individuals predisposed to develop cardiomyopathy could be identified.

Etiology

IDC has been attributed to virtually every known disease mechanism. For example, IDC may be the terminal stage of viral myocarditis. The supporting evidence linking viral myocarditis to IDC is indirect and largely based on animal models. A viral-like illness preceeds the onset of IDC in only 20% of patients.

However, if the illness begins with a fever, a high titer of Coxsackie B virus is often detected. The role of viral myocarditis in IDC is unknown.

Circulating antimyocardial antibodies and defective suppressor cell function may be demonstraed in many patients, but the significance and reproducibility of these findings are in dispute (67,86,139,145,208). The evolution of neoantigens on the surface of the myocardium and a subsequent immune response may constitute one mechanism of myocardial injury. This hypothesis supports the use of immunosuppressive therapy for this disease.

The dilated cardiomyopathy due to cobalt in some Canadian beers demonstrated that environmental toxins could cause a dilated cariomyopathy (156,160). There is no evidence currently to support a toxic etiology.

Smoking is associated with dilated cardiomyopathy (111).

It has been suggested that IDC represents the end stage of hypertensive heart disease in which the hypertension resolves as left ventricular failure develops. This hypothesis seems unlikely for 3 reasons: 1) other sequelae of hypertension (retinopathy and nephrosclerosis) are usually absent, 2) hypertension is seldom associated with IDC, and 3) chronic pressure load usually causes concentric hypertrophy which is not the picture of dilated cardiomyopathy.

In China cardiomyopathy may be due to dietary selenium deficiency (Keshan disease). Although cardiomyopathy has been attributed to generalized malnutrition, there is currently little evidence for dietary deficiencies causing a dilated cardiomyopathy. There are rare reports of familial transmission of IDC, but, in contrast to hypertrophic cardiomyopathy, it is rare.

Clinical presentation

Patients may have a dilated LV for months or years prior to the gradual development of symptoms. The disease is most common in middle-age men. The insidious development and relentless progression of CHF is typical; acute pulmonary edema is not common. Patients usually present with symptoms of elevated left atrial pressure including paroxysmal nocturnal dyspnea, orthponea and dyspnea at rest. Fatigue is very common. These patients often have chest pain that is not typical for angina. Systemic emboli are common and may be a presenting symptom. Likewise, arrhythmias may be the primary symptom or provoke worsening CHF. In the late stages, chest pain and SOB may be due to pulmonary embolism.

The physical exam reveals a normal blood pressure sometimes associated with a tachycardia and a low pulse pressure. Pulsus alternans may occur but pulsus paradoxus is uncommon. Late in the course of the disease the patient is cachectic. The carotid pulse may be of low volume and amplitude. The internal jugular vein may be distended and the presence of prominent V waves indicates end stage tricuspid regurgitation. The apex is laterally displaced, and paradoxic splitting is common due to left bundle branch block. Pulmonary hypertension may be associated with a promnsnt P2. An S4 is common at all stages of the disease and an S3 develops in the later stages. A systolic murmur due to mitral regurgitation is common, and tricuspid regurgitation develops in the late stages. The liver may be enlarged, tender and pulsatile. These findings along with

ascites, peripheral edema and a generalized wasted appearance are late and ominous findings.

Laboratory evaluation

The electrocardiogram is always abnormal. It often shows left bundle branch block, left ventriculr hypertrophy, left axis deviation, left atrial enlargemnt, intraventricular conduction defect and nonspecific ST and T wave abnormalities. Low voltage is rare. Right bundle branch block or complete heart block are less frequent. Pseudo-infarct patterns may occur (significant Q waves without infarction) and probably represent extensive fibrosis. Complex and bizarre ventriculr ectopy is often detected. Atrial fibrillation may be present in up to 20% of these patients.

The chest x-ray invariably shows increased left ventricular volumes which may be difficult to distinguish from generalized cardiomegaly due to enlargement of all chambers. Evidence of increased left ventricular end diastolic pressure and increased pulmonary artery pressure with right heart failure is also seen. Thus, upper lobe redistribution, alveolar infiltrates or Kerley B lines may be present. Pleural effusions are common. The azygous vein and superior vena cava are frequently dilated. The aorta is not prominent and valvular calcification is not present.

The echocardiogram may be used to derive a wide variety of indices of poor LV performance such as increased end diastolic dimension, increased end systolic dimenstion, reduced shortening fraction, etc. The echocardiogram is useful for exclusion of large pericardial effusions or valvular heart disease, and identification of restrictive or hypertrophic patterns. Wall motion abnormalities in IDC may be regional and mimic the consequences of coronary artery disease. THe myocardium appears thin relative to ventricular volume, but wal, thickness is usually normal or slightly incresed. Wall excursion is reduced. Valve motion indicates a reduced cardiac output: reduced opening velocity of the mitral valve and early closure of the aortic valve. The ventriculogram (radionuclide, echo, contrast) does not distinguish coronary disease from dilated cardiomyopathy.

Similarly, the radionuclide ventriculogram will show a reduced ejection fraction below 0.40. Increased end systolic and end diastolic volumes may be measured. The contrast ventriculogram will also demonstrate these abnormalities and allow quantitation of the severity of mitral regurgitation, a common associated finding. If it is uncertain whether mitral regurgitation is the cause or the consequence of a cardiomyopathy cardiac catheterization with ventriculography is essential.

Coronary arteries are normal.

Cardiac catheterization usually demonstrates elevated pulmonary capillary wedge pressure and left ventricular end diastolic pressure (LVEDP). Right heart diastolic pressures may also be incresed but equalization of right atrial and pulmonary capillary wedge pressures is not common. The right ventricular systolic pressure is usually at least 3 times the right ventricular end diastolic pressure (23,26). Cardiac output is usually in the low normal range (cardiac index about 2 to 2.5 L/min).

The value of cardiac biopsy is limited by the absence of specific features that distinguish among the various dilated cardiomyopathies, as described in section 5.

Prognosis and therapy

About half of the deaths are due to progressive heart failure. The remainder are sudden. Mortality in the first year is 20% or higher. The usual course is of progressive deterioration with death within 5 years of diagnosis. However, the Mayo Clinic has emphasized that 25% will live for more than 10 years and will experience functional improvement. Other groups have made similar observations. Otherwise, the clinical course is recurrent heart failure, pulmonary and systemmic emboli, atrial and ventricular arrhythmias, and sudden death.

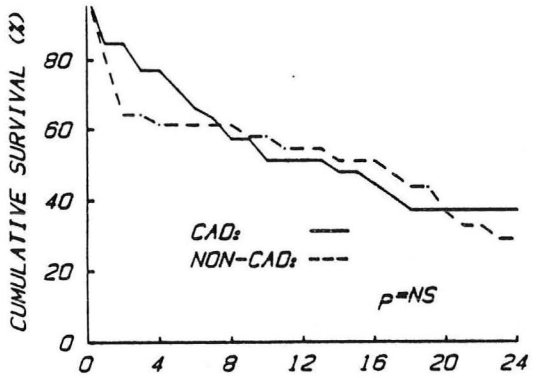


Figure 8. Cumulative survival rates for patients with IDC and patients with failure due to coronary disease. In both groups the prognosis is very poor: 50% one year survival.

The interpretation of Holter monitor data in these patients is controversial. Wilson et al. found tht ventricular ectopy did not predict sudden death, but that complex ectopy was more frequent in patients in NYHA functional class IV. They concluded that antiarrhythmic therapy should probably not be based solely on results of ambulatory monitoring (xx). Similarly, Von Olshausen et al. studied a group of patients without coronary disease with a dilated cardiomyopathy. The mean ejection fraction was 0.35 and all patients had ventriculr ectopy which was Lown grade 3 or higher in 95%. All of the patients that died in the first year of follow-up had an ejection fraction less than 0.4. Ventricular ectopy did not differentiate between patients that die of CHF or those with sudden death. However, Meinertz et al. did find a correlation between ectopy and survival.

Semiquantitative scaling of biopsy specimens may establish prognosis (see section 5).

PERIPARTUM CARDIOMYOPATHY

The diagnosis of congestive heart failure due to postpartum or peripartum cardiomyopathy requires three criteria: 1) failure presents in the last month of pregnancy or in the first 6 months of the postpartum period, 2) prior heart disease is excluded, and 3) other causes of heart failure are ruled out (30,115). Peripartum cardiomyopathy cannot be diagnosed outside this temporal window. If failure develops at a different time, another heart disease must be present. The diagnosis of peripartum cardiomyopathy is important because patients with preexisting heart disease may develop failure for the first time during pregnancy. Failure occurs because of blood volume expansion, increased metabolic demand leading to increased cardiac output, and decreased peripheral resistance.

In addition to prognosis, this dignosis carries important consequences for later pregnancies which must be discussed carefully and thoroughly with the patient.

Risk factors

Several risk factors for development of peripartum cardiomyopathy in North America have been suggested (Table 2). The disease certainly occurs in white and Asian women, but appears to be more common in blacks. In most series the age at presentation is approximately 25% less than 25 years old, 25% between 26 and 30 years, and 50% or more over 30 years old. In various series 80-100% of the patients have had at least one pregnancy. Twin pregnancy may predispose to peripartum cardiomyopathy. The role of hypertension is unclear in the pathogenesis, but it is often present at the time of diagnosis. Patients with toxemia may present with hypertension and volume overload that may be very difficult to distinguish from dilated cardiomyopathy. Some reports have emphasized the impoverished circumstances of these patients, and suggested that malnutrition played a role. However, specific nutritional deficiencies have not been established.

Table 2. Risk factors for developing peripartum cardiomyopathy.

Race: black
Age: > 30 years
Parity: more than one previous pregnancy
Hypertension
Nutritional deficiency

Etiology

The concept of peripartum cardiomyopathy as a distinct entity has been questioned because of the lack of a specific pathological diagnosis. It has been suggested that pregnancy unmasks an underlying cardiomyopathy. However, two features of the disease strongly suggest that it represents a distinct entity. First, dilated cardiomyopathy is very unusual in young women. Its clustering in the peripartum period suggestes a disease related to pregnancy. Second, heart failure due to preexisting disease usually presents around the eighth month of pregnancy when cardiovascular demands are highest. Peripartum cardiomyopathy usually presents one or two months later. In Africa the syndrome may be due to physiological high output state which is a different process from that in North America, and it implies a much better prognosis.

Clinical presentation

The usual onset is within two months after birth. Less commonly, CHF will develop in the last month of pregnancy (Figure 9). The usual symptoms and signs of CHF such as orthopnea, dyspnea, fatigue, edema, an S3 and a systolic murmur are quite common in late pregnancy, and must be distinguished from the normal circulatory events. Occasionaly, pregnancy is complicated by catastrophes which must be differentiated from peripartum cardiomyopathy (Table 3).

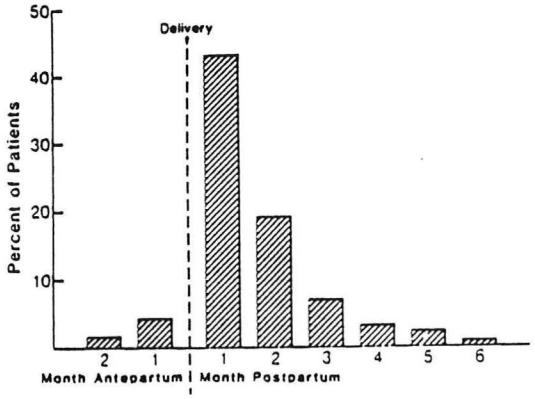


Figure 9. Relationship between time of delivery and onset of symptoms of peripartum cariomyopathy (from ref 115).

Table 3. Differential diagnosis of CHF in late pregnancy.

Toxemia
Pulmonary embolism
Amniotic fluid embolism
Myocardial infarction / coronary dissection
Aortic dissection with aortic insufficiency
Drug reaction

Prognosis, risk of recurrence, and therapy

Overall, mortality for the mother is very high, ranging from 20 to 60% (61). There are two possible clinical courses. In about 50% of patients the heart size returns to normal and long-term prognosis (in the absence of another pregnancy) is good. In the remainder, the heart progressively dilates and intractable failure culminates in death. The risk of recurrence with another pregnancy is increased if heart size does not return to normal in 6 months. DeMakis et al. suggest that cardiomegaly for more than 6 months is a contraindication to future pregnancies. Even in the absence of residual cardiomegaly the mortality rate during subsequent pregnancies is 14%. Recurrence of peripartum cardiomyopathy is possible even if the patient completes an intervening normal pregnancy (61). There is little information about infant mortality or complications in this syndrome, but some authorities estimate a 10% infant mortality rate.

Conventional therapy for congestive heart failure should be employed. If a pulmonary or systemic embolism can be confirmed, anticoagulation with coumadin in the post partum period or with heparin during pregnancy is appropriate. Treatment should be continued for 3 months. Prophylactic therapy is probably not appropriate during pregnancy.

Melvin et al. have recently suggested that endomyocardial biopsy should be used to document myocarditis prior to antiinflammatory therapy with azathioprine and prednisone. The role of myocarditis in this disease is unknown, and the benefits of this therapy have not been documented in controlled trials.

CARDIOMYOPATHY ASSOCIATED WITH PROLONGED ALCOHOL ABUSE

Alcoholic cardiomyopathy refers to a dilated cariomyopathy in a patient with a long history of alcohol abuse. A more appropriate term is alcohol associated cardiomyopathy since a cardiomyopathy due to prolonged ethanol ingestion has not been demonstrated in animal models and does not regularly occur in humans (32,33). In fact, it is remarkable that so many individuals drink with impunity. Throughout the world, excepting the Muslim countries, ethanol consumption is common, and a cardiomypathy is associated with consumption of ethanol in sufficient quantity in any form. The heart disease is thought to be

due to ethanol and its metabolic products. The disease probably does not occur unless the patient has ingested at least 500 grams of ethanol per week for 5 years. Typically a 12 oz can of beer contains 11 grams of ethanol, a bottle of wine contains about 90 grams, and a 750 ml bottle of distilled spirits (80 proof) contains 300 grams. The disease is distinct from cobalt (beer drinker's) cardiomyopathy and beriberi. The heart is indistinguishable from IDC by gross and histological techniques.

Etiology

The association between heavy ethanol consumption and myocardial disease is well established, but for any given exposure to ethanol in humans there is a wide spectrum of myocardial injury (229). This observation suggests that other factors govern individual susceptibility, and emphasize that the pathogenesis of alcohol associated heart disease is not clear (3,4,101,192,193,206). A direct toxic effect of ethanol on the heart is established, but the effect depends on previous exposure to ethanol and concommittant heart disease. For example, in alcoholics a larger dose is required to produce myocardial depression. Patients with cirrhosis may not have overt heart disease, but invasive studies may demonstrate significant LV dysfunction (4). The marked male predominance (even considering the male-female ratio among alcoholics) suggests a marked sexual predisposition to the cardiac effects of ethanol.

Ethanol is metabolized to acetaldehyde and ultimately to acetate ($CH_3CH_2OH \rightarrow CH_3COH \rightarrow CH_3CO_2H$). Acetaldehyde may be very important in the pathogenesis of cardiac damage, via several mechanisms. Acetaldehyde in concentrations detected after moderate ethanol ingestion causes release of myocardial stores of catecholamines. As discussed in section 8, chronic exposure to catecholamines may be deleterious. Ethanol may also impair mitochondrial function and mitochondrial protein synthesis (210). Alcohol reduces the FFA uptake by the left ventricle, but triglyceride uptake is increased (193,252). There are substantial lipid deposits in the alcoholic heart which may be toxic. Isocitrate and malate dehydrogenase leak into the coronary sinus which suggests a membrane defect in these patients.

Clinical presentation

The patient typically is a man, 35-55 years old who has consumed alcohol for 5 to 10 years. Most patients are smokers, but there are not other risk factors for coronary disease. These patients usually have good diets, and do not have overt liver disease, skin findings or the neuropathy associated with the vitamin deficiencies of alcoholism. The first symptoms are usually orthopnea and dyspnea. Atypical chest pain occurs in 25%, and palpitations are quite common. The physical exam does not provide any diagnostic findings to establish the diagnosis. The exam is typical of a patient with dilated cardiomyopathy. Often there is mild diastolic hypertension, tachycardia (due to atrial fibrillation in 12%), and mild jugular venous distension. Rales, an S3 and S4, mitral regurgitation and peripheral edema are present to a variable degree depending on the extent of CHF. Hepatomegaly may be present, but ascites and telangiectasias are not common. Cirrhosis is unusual.

The chest xray is nonspecific and shows 4 chamber enlargement with evidence for elevated left and right atrial pressure. Similarly, the electrocardiogram is not specific (21,48,189). All patients have abnormal ST and T wave abnormalities.

Left ventricular hypertrophy, biatrial abnormalities, premeture beats and atrial fibrillation are common. Cardiac catheterization shows the features of a dilated cardiomyopathy. Significant coronary artery disease is absent. The liver function studies may be abnormal, but these are a consequence of righ and left heart failure; LFTs will improve as the heart failure is treated.

Prognosis and therapy

Prognosis is controlled by the patient's further drinking habits. The cornerstone of therapy is complete abstinence (60). More than 50% of abstaining patients show clinical improvement. Prolonged bedrest has been suggested, although distinguishing the benefits of bedrest from abstention is difficult. These patients should be treated with thiamine and other vitamins. Other aspects of therapy are outlined in section 10. Patients who do not abstain should probably not be treated with anticoagulants. Otherwise, the high risk of emboli is probably reduced by chronic anticoagulation of patients with marked dilation.

5. ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy (EMB) is available in most hospitals with a cardiac catheterization lab. A wide variety of myocardial diseases may be established by biopsy (Table 4), and it is clearly useful for management of patients after cardiac transplantation, planning anthracycline therapy or distinguishing constrictive pericarditis from restrictive - obliterative disease. However, its clinical value for the evaluation of patients with dilated cardiomyopathy remains controversial. This section will review the identification of morphologic lesions in biopsies from patients with dilated cardiomyopathies.

Table 4. Pathologic diagnoses by endomyocardial biopsy

myocarditis	transplant rejection
anthracycline toxicity	hypertrophic myopathy
sarcoid	hemochromatosis
amyloidosis	endomyocardial fibrosis
Fabry's	endocardial fibroelastosis
glycogen storage disease	carcinoid
tumors	Kawasaki's disease
rheumatic fever (245)	

Twenty five years ago Sakakibara and Konno describe transvenous endomyocardial biopsy (207). Cardiac biopsy previously had been performed through a thoracotomy, mediastinotomy, or as a percutaneous needle biopsy. The obvious problems (pain, operative morbidity, poor samples) prompted them to develop a transvenous approach for biopsy of the heart. The Konno bioptome and the vascular approach provides the advantages of current EMB technique: multiple large samples, low risk and morbidity, and the possibility of repeated biopsy. The major disadvantages of this early technique (the large size required venotomy or arteriotomy, and the instrument was quite rigid) have been overcome. The newer bioptomes (King's, Stanford, gastrointestinal bioptomes) provide for percutaneous insertion and easy manipulation in the heart.

Two techniques for right ventricular EMB are considered standard (151). Under fluoroscopic control the bioptome is passed from the right internal jugular

into the right ventricle where the jaws are opened, advanced against the septum, closed and withdrawn. The approach from the femoral vein requires insertion of a long sheath into the right ventricle through which the bioptome is passed. Again, under fluoroscopic control the jaws are opened, the bioptome is advanced against the septum, closed, and forcefully pulled back. The latter technique is used at Parkland and the Dallas VA hospitals.

The patient may feel a twinge of pain during the biopsy, but the procedure is generally associated with little discomfort (87,149). Transient right bundle branch block and ventricular tachyarrhythmias may occur. EMB is safer than renal or liver biopsy. Death occurs in less than 0.03% of cases. Complications include: perforation and tamonade (0.1 to 0.4%), sustained arrhythmia (<0.1%), sustained bundle branch block (<0.1%), and consequences of the jugular approach such as Horner's syndrome, laryngeal nerve paralysis and pneumothorax, all of which complicate less than 0.1% of biopsies.

Two problems are inherent in the interpretation of the biopsy. Artifacts may be produced by the procedure, and multifocal lesions may not be sampled. Artifacts may be produced by the bioptome which squeezes the tissue and tears the edges of the sample. Although fixation is immediate, other artifacts (myocyte separation, hemorrhage, contraction bands) are inevitable. The experienced pathologist examining multiple serial sections of several tissue samples will identify artifacts, but sampling error cannot be excluded.

Three to five biopsies are usually obtained; each is only 1 to 3 cubic mm. Several diseases (myocarditis, toxoplasmosis, sarcoidosis) tend to be focal, and biopsy of the appropriate site may be a chance occurance. Other diseases (hemochromatosis) may be epicardial (83). It has been suggested that five samples improves the accuracy of biopsy to 85%, nevertheless, a negative biopsy does not exclude disease. It is generally accepted that dilated cardiomyopathies may be evaluated with biopsies of the right ventricular septum (even if dysfunction is solely left ventricular) since the right ventricular septum is representative of tissue in the left ventricle (17). This conclusion, however, has again been questioned (56).

Another consideration is that a single biopsy represents only one sample of a condition with a protracted time course. Animal studies indicate that histologic evidence of myocarditis usually resolves after the first month of infection. Several clinical studies with a high rate of detection of myocarditis (e.g., Dec et al. found myocarditis in 67%) perform the biopsies very early (within the first 2 months) of the illness.

The typical clinical problem is a patient with dilated cardiomyopathy without an established etiology. The clinical question is the presence of myocarditis. The pathologist will usually find one of two general pictures in this situation. Idiopathic dilated cardiomyopathy shows the features discussed in section 1: cellular hypertrophy, interstitial fibrosis and perivascular fibrosis. The diagnosis of myocarditis is now determined according to the criteria in Table 5. These criteria were established in 1984 by cardiac pathologists at the Dallas meeting of the American College of Cardiology. Their objective was to introduce uniform definitions for the interpretation of cardiac biopsies (8).

Table 5. Pathologic diagnosis of myocarditis (Dallas criteria)

One biopsy

Active myocarditis
1. Inflammatory infiltrate
2. Necrosis or degeneration of adjacent myocytes (may be vacuolization and irregular cell outline)
3. Fibrosis (sometimes)
4. Uninvolved myocardium is normal

Nonspecific myocarditis
The presence of an inflammatory infiltrate without myocyte damage is not myocarditis and is felt to be nonspecific and consistent with idiopathic dilated cardiomyopathy.

Serial biopsies

Ongoing myocarditis - The myocarditis is persistent and equal to or more prominent than the original biopsy.

Resolving myocarditis - The inflammatory infiltrate is reduced.

Resolved myocarditis - No infiltrate remains and cellular necrosis cannot be detected.

The value of EMB in the management of a patient with dilated cardiomyopathy remains an open question (see section 6: the myocarditis trial). Even if the patient is not a candidate for immunosuppressive therapy (because of coexistant medical problems or the judgement by the physician that it is worthless), it has been suggested that the biopsy may predict the clinical outcome of IDC.

Prognosis of dilated cardiomyopathy: role of EMB

Most authors agree that NYHA functional class III or IV heart failure caries a poor prognosis. All groups agree that duration of symptoms carries little prognostic significance. Hemodynamic indicators are obviously interelated, but there is no single hemodynamic finding that established prognosis. Generally, patients with very poor left ventricular function (ejection fraction less than 20%) do not survive more than 2 years. It is perhaps not surprising that there is a poor correlation between contractile state and mortality since so many patiens die suddenly (i.e., not of pregressive heart failure). Developing an index of prognosis is important because two therapies (vasodilators and heart transplannts) effectively prolong survival. Patients with a poor prognosis perhaps should be treated earlier and more aggressively.

The value of EMB in predicting survival has been evaluated in several longitudinal studies. The techniques for assessing clinical state, pathological criteria for analysis of specimens, and the patient populations differ among the studies. In some cases assessment of LV volumes were imprecise. Generally, these

reports show that evaluation of LV function by objective techniques is a poor indicator of survival. Ventricular ectopy is very common, but is not a good predictor of mortality. Morphometric analysis of biopsies may provide prognostic information about a population. The results of one optimistic study are summarized in Table 6 and Figure 10 (81).

Table 6. Morphometric findings in patientes with IDC: relation to hemodynamics

	Fiber diameter	Myofibril volume
Early death (<2 years)	21.3 u	49.8
Deterioration	20.8 u	54.8
Stable	18.1 u	64.2

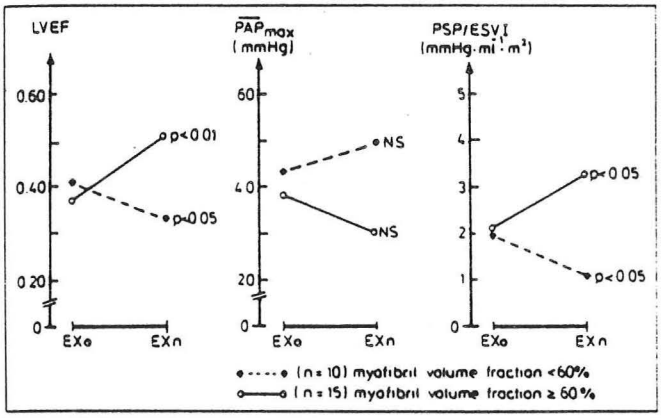


Figure 10. Relationship of morphometic criteria to hemodynamics.

Most studies of EMB have investigated the relationship between morphology and heart disease or hemodynamics. Recetnly the relationship between left ventricular [ATP] and systolic function were studied in patients with CHF. Surprisingly, there was a strong positive correlation between ejection fraction and [ATP]. This study suggests that metabolic rather than structural information may be obtained by EMB (20).

EMB is safe, and it is the only method to establish myocarditis. For practical purposes this is the diagnosis of interest in a patient with dilated cardiomyopathy. Thus, the value of EMB depends on the physician's assesśment of immunosuppressive therapy for myocarditis. Although this approach is not established as effective, dramatic anecdotal reports encourage the use of azathioprine and prednisone for these patients (see below). EMB is not essential for evaluation of dilated cardiomyopathy unless the physician will use the information to guide therapy.

EMB is necessary for the evaluation of rejection of the transplanted heart and assessing anthracycline toxicity. Infiltrative disease (amyloid, etc.) may be excluded in a patient with constrictive physiology. EMB should also be performed if cardiac involvement by a systemic illness is suspected. Its major utility in the typical internal medicine practice is the evaluation of myocarditis. Usually, the shorter the history of failure the greater the chance that myocarditis will be detected. The major contraindications are ventricular masses or bleeding

diathesis. Routine biopsy of all patients with dilated cardiomyopathy is not appropriate.

6. MYOCARDITIS

Myocarditis refers to inflammation of the heart muscle. Pericarditis may be associated, but pericardial disease does not play a role in the hemodynamic consequences (although chest pain may be due to pericarditsi). Myocarditis has been attributed to many infectious agents, although rheumatic myocarditis, viral myocardits, toxoplasmosis myocarditis, and Chaga's disease are perhaps best known. Infectious myocarditis may in principle attack the myocardium in 4 ways: 1) direct invasion of the myocardium, 2) production of a myocardial toxin, 3) stimulation of production of an antigen which cross reacts with myocytes, or 4) interaction with the myocyte to produce a cell surface neoantigen which is the target of the immune response.

Myocarditis may present as the gradual development of congestive heart failure without a history consistent with previous infection, or the first episode may be rapidly progressive congestive heart failure followed by shock and death (205). Chest pain not typical of angina may be present. Heart failure is evident on physical examination. Tachycardia out of proportion to heart failure may indicate myocarditis. The ECG shows nonspecific ST and T wave abnormalities. Minimal to massive cardiomegaly with pulmonary congestion is detected by chest x-ray. Gallium-67 scanning may indicate myocarditis. If the myocarditis is due to viral infection the virus may be isolated from excretions or identified by a fourfod rise in viral titers. Other etiologies of myocarditis (hypersensitivity and chemical myocarditis) are rare and are reviewed elsewhere. Treatment of acute myocarditis is symptomatic and supportive.

The question of myocarditis is usually raised when a patient presents with a dilated cardiomyopathy and symptoms for less than 6 months. Clinical criteria are inadequate to distinguish myocarditis from idiopathic dilated cardiomyopathy. The distinction would be important if specific therapy (immunosuppressive agents) is beneficial. Unfortunately, the clinical value of immunosuppressive therapy for myocarditis is uncertain. In other words, no one knows if it is worthwhile to make the diagnosis of myocarditis. Thus, the decision to proceed with biopsy depends on the physician's judgement of the potential for benefit from immunosuppressive therapy. Typically,
immunosuppressive therapy consists of prednisone and azathioprine.
Because of the risks of this therapy, all agree that immunosuppression for myocarditis should be instituted only after the diagnosis is established by EMB.

Several uncontrolled longitudinal studies have reported benefit from immunosuppressive therapy in myocarditis in 50% of patients (Table 7). Daly et al have reported early improvement in some patients followed by relapse and rapid deterioration in spite of continued therapy.

Table 7. Azathioprine and steroid therapy for myocarditis documented by EMB. The patient's in Melvin's study had peripartum cardiomyopathy. There was no follow-up of three of Zee Cheng's patients; these were removed from the treatd group.

		outcome		
	patients treated	improved	no change	deteriorated or died
Daly	9	4		3
Edwards	5	3	2	
Fenoglio	14	7	7	
Mason	7	4	2	1
Melvin	3	3		
O'Connell	15	6	9	
Zee Chang	8	5	4	
total	61	32	24	4

A major problem in the interpretation of the studies is the lack of a control group when spontaneous improvement is common. Dec et al. studied patients with acute idiopathic cardiomyopathy (symptoms for less than 6 months). All had EMB and myocarditis was present in 18/27. Of the patients with myocarditis the rate of spontaneous improvement (40%) was the same irrespective of treatment with steroids and azathioprine. Figulla et al. reported a spontaneous improvement in 52% of his patients. The arguements for and against immunosuppressive therapy for clinical myocarditis are summarized in Table 8.

The Myocarditis Trial

The National Institutes of Health and the University of Utah are conducting a trial of immunosuppressive therapy for myocarditis to determine if the spontaneious remission rate is altered by immunosuppressive therapy. To be eligible these patients must have symptomatic heart failure for less than two years that is not attributable to a specific cause after evaluation, an active myocarditis documented by EMB, and an ejection fraction < 0.45. In addition to conventional therapy, patients will be randomly assigned to no additonal therapy, the addition of prednisone and azathioprine, or the addition of prednisone and cyclosporine. The study is now underway, and patients will be enrolled until 1989.

Table 8. Treat inflammatory myocarditis with steroids and azathioprine?

YES

1. Continued myocardial damage is immunologically mediated, therefore, suppress the immune system.
2. In uncontrolled studies, patients respond dramatically to immunosuppressive therapy.

NO

1. The mechanism of dilated cardiomyopathy in humans is not known. In experimental animals, steroids may worsen the disease.
2. Steroids carry a risk of fatal infection.
3. Myocarditis may improve spontaneously. Certainly, no controlled studies have shown benefit.

VIRAL MYOCARDITIS

In North America Coxsackievirus Group A and B and some echoviruses are the common agents of viral myocarditis (1,10). These enteroviruses may cause a fatal myocarditis in the neonate. Acute viral myocarditis in the adult is uncommon and probably more benign than in children.

The symptoms of acute viral myocarditis are highly variable. The disease begins with fever and myalgias associated withan upper respiratory or gastrointestinal symptoms. Pever may remain high for up to two weeks. Chest pain is common, but the nature is difficult to categorize. There may be persistent fever with tachyucardia out of proportion to the temperature, and rarely bradycardia. Papillary muscle dysfunction may be associated with MR. Associated orchitis suggests coxsackie B infection. Heart failure may progess rapidly.

The chest x ray shows cardiac enlargement and failure. The ECG is always abnormal, but the findings are nonspecific: ST and T abnormalities. White cell count and ESR are often elevated. Gallium-67 scanning may be abnormal. Sera for viral titers may be obtained and the appropriate excretions may be cultured to document the viral infection. Most patients recover completely, although a few develop a chronic dilated cardiomyopathy. The value of steroids in this disease is controversial. Some animal experiments suggest potentiation of the diseas process by steroids. Nevertheless, some clinicians recommend their use. A recent study of prednisone for IDC showed no benefit.

TOXOPLASMOSIS

Toxoplasmosis is a sporadic cause of myocarditis. Its manifestations are nonspecific and consist of heart failure with hypotension, arrhythmias and AV block. The anitbody titers are high or rise rapidly after presentation with heart failure. They should be obtained if there is a high index of suspicion. Pyrimethamine and sulfonamides may be used, but the response to therapy is unclear.

CHAGA'S DISEASE

Chaga's disease occurs in Central and South America. The disease is due to infection by the intracellular protozoa, Trypanosoma cruzi. It is transmitted by triatomae, or Reduvid bugs. The disease has 3 clinical phases: acute, latent and chronic.

The acute phase may be marked by symptoms of generalized infection such as sweating, fever, nausea, myalgias and lymphadenopathy. Symptoms of myocarditis (similar to viral myocarditis) may also occur. Occasionally the site of innoculation (Romana's sign or the innoculation chagoma) may be detected. Although most patients are not detected during this phase, death due to progressiv CHF may occur; pathological examination shows an extensive myocarditis.

The latent phase lasts 15 to 25 years during which the patient is generally asymptomatic.

The third phase of Chaga's heart disease itself has 3 presentations: asymptomatic, arrhythmic and myopathic. The asymptomatic patients have right bundle branch block, atrioventriculoblock and ST and t wave abnormalities. Patients with arrhythmias have a high incidence of sudden death associated with ventriculr ectopy and fibrillation. The dilated cardiomyopathe is asssociated with right bundle branch block and left axis deviation. Death due to progressive CHF typically occurs within one year. There is no specific therapy.

AIDS

AIDS has been thought to spare the heart with the exception of pericardial disease due to Kaposi's sarcoma. However, a recent study found myocarditis in 38% of autopsied AIDS patients. Of the patients with clinical cardiac dysfunction (vetnricular tachycardia or dilated cardiomyopathy) all had myocarditis (197). The diagnosis of myocarditis during the lifetime of a patient with AIDS is of dubious value since therapy with azathioprine and steroids would be difficult.

7. OTHER ASSOCIATIONS WITH DILATED CARDIOMYOPATHY

ISCHEMIC CARDIOMYOPATHY

This term describes patients who have suffered multiple infarctions which has resulted in a dilated cardiomyopathy. This diagnosis is usually apparent from the history, but it can be difficult if previous infarctions have been silent (27,57,58,123,124). As noted previously, some patients with dilated cardiomyopathy have regional wall motion abnormality and the contrast ventriculogram or echocardiogram cannot be used to absolutely distinguish the early stages of IDC from early ischemic (or multi-infarct) cardiomyopathy.

IRON STORAGE DISEASES

The heart disease of hemochromatosis is rare but very important because it is one of the few reversible causes of myocardial cell damage (54,221). Patients may present with a dilated cardiomyopathy (sometimes a restrictive cardiomyopathy), and therapy directed at iron removal will generally be effective. In the absence of specific therapy, mortality is high.

Hemochromatosis may be primary or secondary. Primary hemochromatosis is due to increased absorption of iron by the intestine. This is a single-gene cardiomyopathy associated with HLA groups A3 and B14. As a consequence of increased absorption, iron is deposited in the heart, liver, skin and pancreas. Cardiomyopathy, cirrhosis and hepatoma, hyperpigmentation and diabetes mellitus are the clinical consequences. Hypogonadism is also a feature. Close relatives have defective iron absorption, and an abnormal serum ferritin is an indicator of the carrier state.

Secondary hemochromatosis develops after repeated transfusions for nonhemorrhagic anemia. Some cases of hemochromatosis are associated with alcoholism, so the evaluation of heart disease must distinguish between these effects. The iron load of 1 unit of blood is 250 mg; cardiac damage requires about 25 grams of iron, or 100 units of blood.

The accumulation of iron over a long latent period leads to deposition of iron, or hemosiderosis, which implies no functional impairment. The clinical syndrome of heart disease due to iron overload is cardiac hemochromatosis. The mechanism of iron damage to the myocyte is not known, but at least one hypothesis has been advanced. Lysozymes isolated from the liver of patients with hemochromatosis are more fragile than normal, and it has been suggested that free iron radicals stimulate lipid peroxidation of intracellular membranes. Pathologically, here is marked dilation of all chambers of the heart and an increased heart mass. The heart tends to feel stiff and the myocardium, especially the left ventricle, has a rust-brown appearance.

The typical patient with primary hemochromatosis is a man over 40 years. Patients, usually younger men, may present solely with cardiac findings in about 15% of cases. The younger the patient, the more likely he is to have a cardiac presentation. The clinical finding is of congestive cardiomyopathy, although a restrictive picture is possible. Most commonly, the presenting findings are the classic triad of hepatomegaly, diabetes mellitus and skin pigmentation. Impotence and loss of libido are frequent. Prior to the availability of insulin the mortality of hemochromatosis was due to complications of diabetes. It appears that a major cause of death is now heart failure. Malignant hepatoma may occur in the older patient. Mural thrombi may be detected at autopsy, but systemic emboli have not (to my knowledge) been reported. The clinical cardiac picture is dominated by either arrhythmias which are very common or by heart failure. The appearance of heart dilation is associated with very high two year mortality

The laboratory evaluation is diagnostic. The most reliable method is the liver biopsy which provides (through measurement of liver iron) an estimate of the total iron load of the body. Serum ferritin over 1000 mg/ml is diagnostic. High serum iron greater than 180 ug/100 ml and greater than 75% saturation of transferrin are also typical. Chondrocalcinosis may be detected by xray.

There is little information about the hemodynamics of heart disease of hemochromatosis. Generally, it is thought to be a dilated cardiomyopathy picture, although there are reports of a restrictive picture. Cardiac biopsy may demonstrate the iron, but is generally not necessary to establish the diagnosis. The subendocardial muscle generally has the least accumulation of iron which may render EMB unreliable.

Adequate venesection for primary hemochromatosis improves heart function. The normal iron load in the body is 4-5 grams, and is increased to 20-50 grams in hemochromatosis. In most cases removal of about 25 grams of iron is necessary. Since each unit of blood contains about 200 mg of iron, about 125 units are removed over 2 years. Phlebotomy of 500 ml is performed once or twice a week. Phlebotomy is much safer and more convenient than chelating agents which are used only in cases of severe anemia.

Desferoximine mesylate is a chelating agent which removes iron from the circulation and is excreted in the bile and urine. The degree of chelation is increased by ascorbic acid. Subcutaneous or i.m. injections are used. This therapy can remove the majority of the iron load and leads to clear improvement in liver structure and function. Therapy is monitored by measurement of the iron content of the liver from biopsy specimens as a guide to the iron load and therefore the duration of therapy. Prophylactic therapy with subcutaneous desferoximine prevents iron-related heart diseas in patients with thalassemia major. For patients who begin therapy at age 10 desferoximine protects against heart disease.

Reducing the iron load probably will cure the cardiomyopathy and prolong the survival (221). If a patient is identified with primary hemochromatosis, all siblings should be screened. HLA typing, and measurements of plasma iron and ferritin will establish the diagnosis and permit prophylactic venesection.

DIETARY FACTORS

Dietary selenium deficiency is responsible for a dilated cardiomyopathy in China (Keshan disease) which primarily affects young women. One case has been reported in North America in a patient receiving two years of hyperalimentation. Cobalt induced cardiomyopathy is of historical interest.

NEUROMUSCULAR DISEASES

Cardiac disease is an integral part of several inherited neuromuscular disorders (Table 9). The neurological picture is almost always dominant, and it is unlikely that an adult patient without evident neuromuscular disease will present with overt cardiac disease. It is, however, prudent to consider neuromuscular disease in patients with puzzling cardiovascular pictures. Three neurological syndromes have been reported to present with heart block: Kearns-Sayre syndrome, myotonic muscular dystrophy, and Emery-Dreifuss syndrome. Idiopathic dilated cardiomyopathy as a primary presentation occurs occasionally associated with a nonspecific centronuclear myopathy. Duchene's muscular dystrophy is x-linked recessive, and women with dilated cardiomyopathies as the sole manifestation of a carrier state have been described. Therefore, if a woman presents with a cardiomyopathy, determine if her son has Duchene's muscular dystrophy.

Table 9. Cardiac involvement in neuromuscular disease.

Progressive muscular dystrophies

1. X linked (Duschene's)
2. Autosomal recessive slowly progressive (Becker's)
3. Erb's limb-girdle dystrophy

4. Facsioscapulhumoral dystrophy of Landouzy-Dejerine

Myotonic dystrophy (Steinert's disease)
Freidreich's ataxia

ANTHRACYCLINE THERAPY

Cancer chemotherapy with the anthracyclines is associated with a risk of cardiomyopathy. Daunorubicin and doxorubicin produce direct myocardial toxicity by binding mitochondrial and nuclear DNA. The effect is cumulative because release of the drug from DNA is very slow. Transcription of RNA is impaired and therefore protein replenishment gradually is unable to keep up with normal protein turnover in the myocardium.

The cardiomyopathy of anthracycline therapy presents 2 to 6 months after the last dose. Unlike other dilated cardiomyopathies the disease appears not to progress (assuming no further anthracycline therapy). The risk of cardiomyopathy is dependent on the cumulative dose. The continuum of risk ranges from less than 2% at a total dose less than 400 mg/m2 to greater than 20% after more than 700 mg/m2. Unfortunately, routine noninvasive studies may be normal in the presence of biopsy-proven myocarditis, and toxicity may present clinically without histologic evidence of myocarditis. Nevertheless, EMB has been used in some centers to guide therapy.

UREMIA

Uremic cardiomyopathy refers to a dilated cardiomyothic picture that is not due to volume overload which resolves when adequate dialysis is instituted (18,65,118,244).

FAMILIAL DILATED CARDIOMYOPATHY

Unlike hypertrophic myopathies, there is only a weak relationship between family history and dilated cardiomyopathy (24, 157).

SARCOID

Sarcoid heart disease may occur when others organs are only minimally affected. Since it may present as heart failure, it will be mentioned briefly. Patients without other evidence of sarcoid may present with symptomatic arrhythmias and heart block as evidence of cardiac involvement. However, a dilated cardiomyopathy in the absence of other evidence of sarcoid has not been reported. There is one report of diagnosis of sarcoid by biopsy.

DIABETIC CARDIOMYOPATHY

Diabetes has consistently been associted with accelerated atherosclerosis of the large coronary arteries. Recently, the emphasis on coronary artery disease as the only cardiac risk of diabetes has been modified. It is now clear from epidemiologic, clinical and experimental stuties that heart muscle can be affected by diabetes independent of epicardial coronary disease. Although this syndrome is not a dilated cardiomyopathy, it now appears that an early

cardiomyopathy may develop as a consequence of diabetes independent of coronary artery disease.

The relative risk of congestive heart failure in male patients with diabetes compared to patients without diabetes is about 2.4. This relative risk is substantial increased for diabetic women to 5.1. In the absence of clinical coronary artery disease the risk of congestive heart failure is increased about 4 times, independent of other known risk factors. These results from the Framingham study are limited since the patients did not have coronary angiography. Other known risk factors for congestive heart failure do not account for this difference. In patients with adult onset diabetes the incidence of heart failure is high, but the incidence of other coronary risk factors is not higher than an agematched population.

Rubler et al. in 1972 described four patients with diabetes, cardiomegaly, and congestive heart failure. One patient also presented with severe hyperglycemia and uremia. All patients had adult onset diabetes without a history of hypertension or valvular heart disease. One patient died of complications of hip surgery, one died of intractable heart failure, and one died of heart failure and intractable uremia. All were female, and the average age was 64 years (range 49-76). All patients had clinical heart failure without hypertension. The average BUN was 44 mg/100 ml, and the creatinine was 2.6 mg/100 ml. Hypoalbuminemia was minimal. The chest x ray showed cardiomegaly, congestion and pleural effusions. The ECG was nonspecific. At autopsy, all patients had Kimmelsteil-Wilson disese, increased LV mass and volumes, and no coronary artery disease. This group concluded that long standing adult onset diabetes with renal disease may have associated congestive failure and hypertrophy not attributable to hypertension or other known causes of cardiomyopathy.

Hamby showed that in patients with idiopathic cardiomyopathy a large proportion (16/73, or 22%) had diabetes. Three of the patients had autopsies, and the epicardial coronary arteries were free of atherosclerosis. Regan described a small group of patientw with normal coronaries, diabetes and heart failure (Table 11).

Table 11. Ventricular hemodynamics in normal humans and patients with diabetes (data from Regan et al.).

		Diabetics	
	Control	without CHF	with CHF
blood pressure (mm Hg)	115/64	125/78	125/73
stroke volume index (ml)	44	31	24
end diastolic volume (ml)	69	62	78
end diastolic pressure (mm Hg)	8	12	13
ejection fraction	0.53	0.49	0.35

Extensive animal studies have documented a cardiomyopathy which is due to diabetes (15, 72-76, 80, 93-95, 112, 143, 146, 183, 196). In humans a subclinical myopathy may be detected (36,90,158). However, dilated cardiomyopathy in diabetics is almost always attributable to coexisting diseases, and there is little evidence that the subclinical myopathy is significant. Left ventricular dysfunction may develop in diabetic patients independent of typical coronary

atherosclerosis which may be potentiated by hypertension. There is evidence for intramyocardial small vessel disease, but the subclinical complications are probably due to a direct effect of diabetes on the myocardium.

PHEOCHROMOCYTOMA

If a patient presents with a dilated cardiomyopathy, attention should be given to four symptoms: headache, palpitations, excessive sweating, and chest pain which occurs after onset of one of the first three symptoms (19,96). The patient is often thin, and the blood pressure is often labile. Hypertension (diastolic > 110 mm Hg) may be detected, and orthostatic hypotension may be prominent. If neurofibromas are present, pheochromocytoma should be strongly considered. The diagnosis is established by assay for catecholamines and their metabolites in the urine. Definitive therapy of the pheochromocytoma prevents further myocardial damage.

Although a dilated cardiomyopathy is rarely the first manifestation of a pheochromocytoma, patients dying with a pheochromocytoma usually do sustain some cardiac injury. Multiple areas of focal fibrosis are often found in the myocardium of these patients. Van Vliet et al. found active myocarditis in 58% of their patients with a pheochromocytoma and fibrosis in most of the remainder. They noted that the myocarditic lesions were very similar to those induced in rats killed shortly after injection with norepinephrine, and fibrosis in a diffuse pattern appeared in rates killed several weeks after injection. These and other studies have amply demonstrated that chronic exposure to catecholamines (even in the absence of hypertension) may induce cardiac injury.

DRUG ABUSE

Another mechanism for chronic exposure of the myocardium to high concentrations of catecholamines is far more common than pheochromocytoma: abuse of amphetamines or cocaine. A substantial literature has accumulated relating cocaine use to myocardial ischemia and infarction, usually in young individuals without coronary disease (43, 50, 102, 121, 131, 182, 202, 222, 226, 246). These anecdotes suggest a causal relationship between cocaine use and myocardial ischemia. Acute myocardial infarction, reversible ischemia, heart block with myocarditis, and severe ventricular arrhythmias have been described. These complications of cocaine occur with both common routes of administration (intravenous or intranasal), with small doses of the drug, and in the absence of underlying cardiac disease. Dilated cardiomyopathy has been attributed to chronic use of amphetamine and an amphetamine analogue, propylhexidrine (11,35,51,226). Although chronic cocaine use has not been associated with a dilated cardiomyopathy, its association with myocarditis and its effects on myocardial catecholamine metabolism raise this possibility.

Myocardial pathology has been reviewed in patients after cocaine-related deaths. In this autopsy series the presence and severity of contraction bands in the heart was strongly correlated with cocaine level in the blood and urine (233). Focal myocyte contraction bands are hypereosinophilic bands crossing the long axis of the myofibril. They are thought to represent severely contracted and clumped sarcomeres. The presence of contraction bands must be interpreted with great care since some are present in virtually every heart. Although they are nonspecific, they are also prominent in animal models of pheochromocytoma.

The mechanism of formation of contraction bands is not clear, but may be related to catecholamine overload. In addition to indirect effects mediated by the central nervous system, cocaine has direct effects on the heart. At low concentrations cocaine is a membrane stabilizing agent which is electrophysiologically very similar to quinidine. Like the other local anesthetics (procaine, lidocaine, etc.), cocaine depresses conduction of nerve impulses by preventing changes in membrane permeability to sodium. At higher concentrations and unlike other local anesthetics cocaine prevents reuptake of norepinephrine by preganglionic sympathetic nerves. Since norepinephrine is removed from the synaptic cleft by reuptake, cocaine may potentiate all of the effects of norepinephrine. Cocaine is the only local anesthetic which produces sensitization to catecholamines. This effect also produces its vasoconstrictor properties. Chronic cocaine use dramatically increases the norepinephrine content of the left ventricle in experimental animals, although the rate of norepinephrine synthesis is reduced.

Speculative pathophysiology of cocaine-related myocardial injury:

1. Chronic cocaine use blocks reuptake of catecholamines in the heart
2. Myocytes are chronically exposed to increased norepinephrine
3. Catecholamin induced injury (possibly due to calcium overload)
4. Scarring and fibrosis
5. Myopathy or sudden death due to arrhythmias

It should also be noted that patients may have primary heart disease (idiopathic myocarditis, anomalous coronary artery, coronary artery disease, etc.) which may predispose them to arrhythmias induced by cocaine or other drugs.

8. CATECHOLAMINES AND MYOCARDIAL INJURY

Myocardial injury due to epinephrine and norepinephrine has been described repeatedly since the early 1900's. The catecholamines enhance inotropic state, heart rate, oxygen consumption and predispose to atrial and ventricular arrhythmias. During acute hypotension these effects are largely beneficial. However, the chronic activation of the sympathetic nervous system in heart failure may play a major role in the progression of the disease. Blocking some of the consequences of sympathetic activation may offer an avenue for therapy.

Pathologically, the myocardial lesion induced by catecholamines is the same for epinephrine and norepinephrine. The observations in a variety of experimental animals and in patients with pheochromocytoma are similar. Typically, immediately after exposure to high concdentrations of catecholamines the heart develops interstitial edema, glycogen depletion, lipid deposits, and contraction bands. Polymorphonuclear leukocytes appear within hours, and are followed quickly by mononuclear cells. Starting at about 3 days focal necrosis and myofibril disruption are observed. Mild fibrosis may be detected which becomes progressively more prominent. Polymorphonuclear leukocytes are absent at this stage.

The mechanism of catecholamine-induced injury has been extensively investigated (106). Microvascular spasm has been suggested as a pathogenic mechanism in the initiation of myocarditis and cardiomyopathy because it may produce focal necrosis. However, isoproterenol produces a more severe myocardial lesion than epinephrine or norepinephrine, and at a lower relative dose which suggests that coronary constriction may not play a central role. The left ventricle of some other species receives its blood supply through spongy endocardial lacunae which are incapable of vasoconstriction. Isoproterenol causes necrosis in this region. These experiments suggest a direct toxic effect of beta adrenergic stimulation which may be mediated by chronic calcium overload.

These observations do not exclude an effect of ischemia due to supply / demand imbalance or a combination of factors leading to necrosis. In particular, it has been suggested that the lipid deposits associated with catecholamine injury are due to local ischemia. Alternatively, Hoak et al. proposed that these lipid droplets are due to the mobilization of fatty acids from peripheral storage sites. The increased levels of fatty acids lead to deposition in metabolically active tissues and subsequent uncoupling of oxidative phosphorylation due to accumulation of fatty acids. A third hypothesis suggests that intravascular platelet aggregation and microinfarction may be responsible.

9. EVALUATION OF THE PATIENT WITH A DILATED CARDIOMYOPATHY

The initial evaluation of a patient with a suspected dilated cardiomyopathy begins with three questions: Is the problem a cardiomyopathy? What is the hemodynamic class? What is the cause of the cardiomyopathy?

The first symptom of a dilated cardiomyopathy is usually dyspnesa on exertion. It may be useful to note the New York Heart Association functional class because several important studies use this assessment which is summarized in Table 11. Areas of importance in the history are implicit from the previous sections (Table 12).

Table 11. New York Heart Association Functional Classification

I	No limitations. Ordinary activity does not cause symptoms
II	Slight limitation. Ordinary activity results in symptoms
III	Marked limitation. Less than ordinary activity causes symptoms
IV	Symptoms present at rest.

In addition to assessing the severity of heart failure, the elderly patient should be examined carefully for aortic stenosis and evidence of thyroid disease. All patients shoud have routine lab studies, thyroid studies and serum iron and ferritin. The chest x-ray, electrocardiogram and echocardiogram should allow determination of the major hemodynamic class of cardiomyopathy.

Table 12. Important topics in the history of patients with dilated cardiomyopathy.

Alcohol use (question family members)	AIDS
Repeated blood transfusions	Cat exposure
Anthracycline therapy	Pregnancy history
Symptoms of pheochromocytoma	live in S America
Febrile illness and viral syndrome	Drug use

Family history of cardiomyopathy or neuromuscular disease

If the echocardiogram is technically inadequate because of obesity or pulmonary disease, other studies are essential. Further, if the physiological diagnosis is uncertain, cardiac catheteization may be critical. For other questions, coronary angiography is essential. The radionuclide ventriculogram provides diagnostic information as well as a convenient monitor of disease progress. If sarcoidosis is suspected (young patient, history of ventricular tachycardia, bundle branch block or heart block with regional wall motion abnormalities) converting enzyme assay may be useful. Urinay screening studies for pheochromocytoma should be pursued if suggested by the history. Similarly, viral and toxoplasmosis titers may be obtained if the disease is of recent onset or other factors are suggestive. The role of gallium-67 scanning is not clear. EMB should be performed to address specific questions which will alter therapy.

10. THERAPY

Therapy for patients with dilated cardiomyopathy has three objectives: prevent further myocardial damage, alleviate symptoms, and prolong life. Removal of the inciting mechanism(s) is the first step since prevention of cardiomyopathy is better than treatment. The alleviation of symptoms relies largely on treatment of the hemodynamic disorder. Prolongation of life with medical therapy for patients with CHF was, until 1 year ago, not established. Two important studies have since been published, and should in some cases form the basis of therapy.

Primary therapy for CHF refers to a stepped approach to care which applies to most patients. The usual principles of managing congestive heart failure apply. The hemodynamic goal of therapy is usually to reduce left atrial pressure and to increase cardiac output. When left ventricular function is mildly or moderately impaired the dominant symptoms may be pulmonary. Under these circumstance the first line of therapy, sodium restriction and diuretics, will alleviate venous congestion without significantly depressing cardiac output or impairing renal functin. Digitalis may be added. If exertional fatigue or significant pulmonary congestion persist in spite of diuretic therapy to the point of symptom or laboratory evidence of volume contraction, then vasodilators should be strongly considered. The management of these patients in NYHA class III or IV after initial therapy requires familiarity with the concepts of preload and aftreload, their relationship to symptoms, and their response to drug therapy.

PRIMARY THERAPY

One approach may be summarized in 4 steps:

Step 0. Remove the inciting factor(s) including hypertension. Diabetes should be controlled and the patient should stop smoking. Vigorous or exhausting activities should be curtailed.
Step 1. If a patient is in NYHA class II, begin with diuretics and modest sodium restriction.
Step 2. If congestive symptoms persist on a modest dose of furosemide (80 mg/day), or if fatigue is a prominent symptom, add digitalis
Step 3. If a patient remains in NYHA class III or IV after the addition of digitalis, vasodilators should be added.

Adjunctive therapy will be necessary in special cases.

Diuretics

The foundation of drug therapy for CHF is furosemide. The usual dose ranges from 40 mg q.d. to about 200 mg t.i.d. Common complications include hypokalemia, hyponatremia, acid-base disturbance, hyperuricemia, etc. Combiningfurosemide with metolazone should be done under carefully controlled circumstances because of the potential for hypokalemia. The dose of a diuretic needed in the first few days of therapy may be too large for maintenance therapy and require substantial reduction.

Digitalis

Digitalis is the traditional drug for congestive heart failure. Impaired myocardial contractility is the fundamental defect of the dilated cardiomyopathies, and correction of this defect would interrupt the cycle of events described in section 1. Its value in patients with sinus rhythm and congestive failure remains controversial. A vast literature may be summarized as follows. Several studies have shown that patients with sinus rhythm on digitalis because of heart failure may be safely withdrawn from the drug. Some of these studies are flawed by poor characterization of the patients and unclear indications fro digitalis in the first place. It is clear that many patients with CHF on digitalis will not suffer if the drug is stopped. Several reports of carefully studied patients demonstrate a beneficial effect of digitalis even when used with diuretics in patients with CHF and sinus rhythm. I will summarize an enormous literature with the following comments:

1. Digitalis has, at best, a modest beneficial effect in patients with CHF and sinus rhythm. This effect is due to its positive inotropic properties. Generally, diuretic therapy is much more effective in controlling the usual signs and symptoms of CHF.

2. If a patient is poorly compensated (rales, edema, S3), do not stop digitalis. Consider stopping the drug only after congestive signs and symptoms have been controlled with other measures.

3. Digitalis is not useful in many patients with CHF. For example, in the study by Arnold et al., widely referenced as showing beneficial effects of digitalis, 4 of 9 patients had no change in functional class when the drug was withdrawn.

In a very recent study digoxin was compared to captopril in patients with moderate CHF on furosemide. Digoxin incresed ejection fraction from 26% to 30% but did not significantly alter functional class or exercise time. Captopril improved functional class and exercise time compared to placebo. The authors concluded that captopril has a primary role in therapy for CHF.

Vasodilators

Vasodilators may be considered in two classes: direct vasodilators such as the nitrates and hydralazine which interact with the vessel, and the indirect vasodilators such as captopril, enalapril and prazocin which interfere with neurohumoral function. This distinction has clinical significance since it predicts that the effectiveness of the indirect agents will depend on the underlying activation of the target neurohumoral system, and that their effectiveness may not increase with increased dose. Hydralazine has a particularly wide dose-response range and it may be necessary to assess its efficacy with direct measurements of wedge pressures and cardiac output. Minoxidil will not be considered because of association with Na retention.

Nitrates are potent vasodilators which, in low doses, are pure venodilators. In higher doses, there is some direct effect on peripheral resistance. Nitrates directly reduce left ventricular filling pressure and improve pulmonary congestive symptoms. There is little effect on cardiac output. In patients with coronary artery disease these agents are especially useful because of their beneficial effect on angina pectoris. Unlike patients with normal left ventricular function and no congestive failure, patients with congestive heart failure seldom develop hypotension or tachycardia. Some patients with severe

failure and edema are resistant to nitrates, but sensitivity to nitrates may be restored by diuretics.

Prazosin blocks the post-synaptic alpha-one receptor. This drug is a balanced venous and arteriolar dilator. In short term studies it reduces LVEDP and improves cardiac output. when used in doses of 5-10 mg po tid. However, in long-term studies of CHF several double blind investigations have shown no persistant benefit. A large fraction of patients develop tolerance.

Hydralazine is a potent arteriolar dilator which has little effect on the LVEDP when used alone in patients with CHF. Although it improves cardiac output when used acutely, long term benefits as the sole therapy are not clear. Generally, it should be used in combination whti nitrates. Hydralazine has substantial side effects which include systemic lupus erythematosis, rash, arthralgias and angina in patients with ischemic heart disease. The usual dose is 75 mg.

Angiotensin converting enzyme inhibitors disrupt the renin - angiotensin - aldosterone system which plays a key role in generating and perpetuating congestive heart failure. In general, these agents reduce peripheral vascular resistance and maintain perfusion of the brain, heart and kidneys. There is little effect on heart rate, and cardiac output is not changed or increases. The side effects are minimal and there is little influence on uric acid, glucose, potassium or lipids.

Two ACE inhibitors are available for use in North America: captopril and enalapril. Both agents improve congestive heart failure. Although there is more experience with captopril because of its use in hypertension, enalapril appears to be as safe. Captopril and enalapril bind angiotensin converting enzyme and block its activity. Unlike captopril, enalapril is a prodrug: after oral administration its ethyl ester is hydrolyzed in the liver to yield enaliprilic acid which is the active inhibitor. The requirement for hydrolysis delays the onset of action of enalapril; its peak effect is not seen until 5 hours after drug administration compared to 1 to 1.5 hours after captopril. It is conceivable that derangements in hepatic blood flow in patients with severe failure may delay this hydrolysis further. Enaliprilate binds seven sites on ACE (compared to five by captopril) which reduces the rate of dissociation.. These features of enalapril's structure translate into slower onset, longer duration of action and less frequent dosing.

Both drugs cause a decrease in peripheral vascular resistance of about 20% and an increase in renal blood flow. Transient renal deterioration develops after initiation of captopril therapy, but appears to improve after about 1 week of therapy.

After measurement of baseline heart rate and blood pressure, captopril therapy is usually initiated at 6.25 mg., and is progressively increased to 12.5 to 50 mg every 8 hours. Because of the near-maximal activation of the sympathetic nervous system, patients with heart failure may be unable to defend blood pressure against the effects of captopril. Thus, symptomatic hypotension may occur even with this small dose in a small number of patients, and close observation is necessary. Higher doses prolong the inhibition of ACE, but they may not provide further improvement in cardiac output.

The serum sodium may be very useful during the initiation of therapy with ACE inhibitors. In patients with CHF the serum Na correlates inversely with the plasma renin activity. Thus, a low serum Na may indicate high levels of renin and angiotensin. If the Na is < 135 meq/L, are likely to have a greater increas in cardiac index and decrease in filling pressure than patients with higher Na. However, these patients are also far more likely to develop hypotension.

Patients selected for vasodilator therapy should have NYHA class III or IV heart failure after therapy with diuretics and salt restriction (and digitalis, to satisfy the criteria of the VA and CONSENSUS trials). The limiting symptoms should be fatigue, dyspnea with extertion, orthopnea or nocturnal dyspnea. A benefit in terms of mortality has not been shown for mild heart failure (NYHA class II), although it may be important (AJC 57:459.). The ejection fraction should clearly be less than 40% to exclude (if you haven't already) patients with diastolic dysfunction masquerading as dilated cardiomyopathy.

Vasodilator therapy and mortality: The VA and CONSENSUS trials

Vasodilators added to digitalis and diuretics have dramatically improved therapy of symptomatic congestive heart failure. These benefits are long term for certain drug combinations. However, until one year ago, there was no clear evidence that survival of patients would be improved by this therapy. Two very important studies have since appeared which show convincingly that peripheral vasoconstriction plays a role in premature death as well as symptoms, and that vasodilators reduce mortality from failure.

The Veterans Administration Cooperative Study (also known as V-HeFT or vasodilatos hert failure trial) enrolled men with mild or moderate heart failure with an average ejection fraction of 30%. These patients were treated with diuretics and digitalis and randomly assigned to one of three treatment arms for additional therapy: 1) placebo, 2) prazosin (20 mg/day) or 3) hydralazine (300 mg/day) + isosorbide dinitrate (160 mg/day). Judged from overall mortality, prazosin provided no benefit. The three year mortality 47% for those patients treated with placebo, and 36% for those patients receiving nitrates plus hydralazine. This represented a 36% reduction in risk of mortality after 3 years. Ejection fraction was measured after 8 weeks and 1 year of therapy; only the hydralazine + nitrate group showed an increase, from 30% to approximately 35%.

This important study provided the first evidence that vasodilator therapy prolongs survival, but the benefit was modest. Unfortunately, the hydralazine + nitrate combination was associated with side effects causing discontinuatioin of therapy in 20% of the patients. Also, many of the deaths (45%) were sudden, again suggesting that arrhythmias rather than progression of heart failure may be the cause of death in these patients.

The second large multicenter study of vasodilator therapy used enalapril (up to 20 mg b.i.d.) in addition to diuretics and digitalis. Results were more impressive than the VA study because the risk reduction in the enalapril group was 31% at one year. The study was stopped prematurely by the Ethical Review Committee about 18 months after the first patient was randomized.

Table 13. Causes of death in the CONSENSUS study.

Cause	Therapy	
	placebo	enalapril
Sudden death	0.15	0.16
Heart failure	0.35	0.17
Other	0.04	0.06
Alive	0.46	0.61

Patients treated with enalapril had the same risk of sudden death as control patients. Thus, the improvement in survival was due to reduction in the progression of heart failure, as summarized in Table 13. In addition to reducing mortality, enalapril improved functional classification of these patients (Table 14).

Table 14. Functional classification of patients from each treatment group in the CONSENSUS study. All patients were in NYHA functional class IV at the time of enrollment into the study. The average follow-up was 6 months.

NYHA class	Therapy	
	placebo	enalapril
I	0.0	0.02
II	0.02	0.10
III	0.20	0.30
IV	0.24	0.16
dead	0.54	0.39
unknown	0.01	0.02

SPECIAL CIRCUMSTANCES

Anticoagulation

Fuster recommends chronic anticoagulation with coumadin for these patients with dilated cardiomyopathies because of the known high rate of systemic emboli. This recommendation for prophylactic therapy must be balanced against the real risks of complications. Unless there are compelling reasons not to treat, documented pulmonary or systemic emboli should be managed with anticoagulation for 6 months. Both atrial fibrillation and dilated cardiomyopathy independently predispose to emboli. Although no controlled studies have shown that patients with DC plus atrial fibrillation benefit from chronic anticoagulation, it seems reasonable to treat these patients prophylactically.

Atrial fibrillation

Atrial fibrillation is one of the most common cardiac arrhythmias, and it has special implications for patients with dilated cardiomyopathy. Atrial fibrillation may worsen both the congestive and low output symptoms of heart failure. It also increases the risk of systemic and pulmonary embolization.

Therefore, maintenance of sinus rhythm is an important objective of therapy for CHF. Selection of appropriate therapy depends on the goal of treatment (slowing the ventricular response or conversion to sinus rhythm) and the urgency of the situation.

If a rapid ventricular responese is asociated with hypotension, pulmonary edema or angina, the patient may be treated with electrical cardioversion or intravenous digoxin, depending on the urgency of the situation. If the patient is relatively stable and atrial fibrillation is of recent onset (< 5 days) pharmacologic cardioversion may be attempted with quinidine or a quinidine - like agent plus digoxin. Electrical cardioversion may later be necessary. If atrial fibrillation has been present for more than one week, the patient should be systemically anticoagulated for at least 2 weeks prior to attempting pharmacological or electrical cardioversion.

The decision to continue antiarrhythmic agents presumes that the benefits of preserving sinus rhythm outweight the toxicity of the antiarrhythmic agents which in many cases is substantial. Disopyramide should not be used in patients with dilated cardiomyopathy. Amiodarone and flecanide may be considered in difficult cases. In extreme siturations endocardial catheter fulguration or surgical division of the atrioventricular node may be necessary.

Ventricular tachycardia and sudden death

The management of ventricular tachycardia in a patient with coronary artery disease, a well - studied problem, is difficult. These problems are compounded in all conditions unrelated to coronary artery disease (because of less experience), and DC is no exception. Ther very high incidence of arrhythmias in these patients has already been noted.

Programmed electrical stimulation appears to have little value in predicting response to therapy (188). The induction and termination of ventricular ectopy by electrophysiologic techniques supports reentry as the mechism of ventricular tachycardia. However, a complete or partial response to therapy was not associated with a better prognosis in patients with DC, an observation that contrasts with experientce in patients with coronary disease. The role of electrophysiologic testing in these patients is uncertain.

A conservative approach would be to treat only symptomatic ventricular tachycardia or fibrillation. An automatic implanted cardiovertor - defibrillator should be considered. Alternatively, one could justify suppressing ventricular ectopy based on Meinertz's observations (154).

Calcium channel blocking drugs

The calcium channel blockers are coronary and peripheral vasodilators and have been used for afterload-reduction therapy. All are negative inotropic agents, however, and might be expected to cause further deterioration in systolic funciton. Compared to verapamil and diltiazem, nifedipine is the most potent peripheral vasodilator and it may have beneficial effects in patients with cardiomyopathy and failure.

Klugman et al. found that 20 mg of nifedipine (sublingual) reduced the systemic vasuclar resistance and increased cardiac output. Other studies have

confirmed this short-term benefit of nifedipine. Belocci et al. found that patientts with moderate CHF maintained the short term benefits for up to two months when given nifedipine 20 mg orlly every 6 hours. However, the results of therapy with captopril was compared to nifedipine in a double blind crossover study of patients in NYHA functional class III or IV with DC. Exercise time, functional class, stroke volume index, pulmonary capillary wedge pressure and pulmonary arter pressure were significantly improved in patients on captopril but not nifedipine. Captopril also decreased left ventricular end systolic wall stress. Nifedipine was associated with dependent edema and weight gain, whereas captopril was associated with a rise in serem creatinine in one patient and transient taste abnormalities in two patients. In general, however, both drugs were well tolerated. The authors concluded that both drugs had similar effects on reducing peripheral vascular resistance, but theis beneficial effect of nifedipine was negated by its negative inotropic effects.

Patients with congestive heart failure can tolerate nifedipine for short or long term therapy. Nifedipine may be particularly useful if coronary artery disease and angina are present. However, its value as standard therapy for CHF is not established.

HEART REPLACEMENT

The artificial heart is not a prectical alternative now. Heart transplantation probably improves survival in patients with IDC. This procedure is limited to the relatively young stable patient without other systemic disease. The current one year survival rate is 80% and the attrition after that is about 5%/year for patients on cyclosporine.
Dilated cardiomyopathy patients account for about 48% of the transplants at Stanford (47% are for ischemic heart disease and 5% are valvular or congenital diseases).

Two questions are particularly important for patients with IDC who are given transplants. First, since these patients tend to be younger than patients with ischemic heart disease, are they more likely to develop neoplasms as a consequence of transplantation? Second, Is there an ongoing process directed against the heart? Survival of patient and graft is no different from patients with ischemic heart disease. Patients with cardiomyopathy do not have more frequent rejection, and they do not have more frequent allograft atherosclerosis.

NEW APPROACHES

Beta adrenergic blockers

Beta-adrenergic antagonists marketed in the United States cary the FDA-mandated warning that their use in congestive heart failure is contraindicated. This warning reflects a traditional view that activation of the sympathetic nervous system is an adaptive or supportive mechanism in heart failure. Certainly, there is a small experience showing that beta-blockers may precipitate heart failure. However, large trials such as the Beta Blocker Heart Attack Trial showed that patients with a history of heart failure tolerated propranolol well, showed no increased risk of heart failure, and, in fact received the greatest benefit from propranolol in terms of reduction in sudden death and recurrent infarction.

The potential for harmful effects of catecholamines on the myocardium are described in a previous section. Catecholamines may injure the myocardium by causing subendocardial or focal ischemia, calcium overload, or increased susceptibility to various processes. In a somewhat radical departure from standard thinking, Waagstein and colleagues reported beneficial effects of beta blockers in heart failure in 1975. Typically, metoprolol, 25-200 mg/day was used. Since that time, dramatic confirmatory reports from the same group have appeared. Particularly impressive is their observation of deterioration when beta blockers are stopped. Unfortunately, none of the Swedish trials contain a control group.

Studies in the United States provide some support for the Swedish observations. A report from the transplant program at Stanford described 4 patients with end stage heart failure who improved so much on beta blockers that they were no longer candidates for transplant. Two randomized studies by Englemeier et al. and by Anderson et al. are promising in terms of symptom improvement, increased exercise tolerance and reduced mortality. Anderson emphasized that most of their patients (80%) tolerated metoprolol in spite of lw ejection fractions. However, they noted that the trend toward improved survival could be due to selection of patients with a good prognosis since they tolerated beta blockers.

A major feature of these studies is their duration: 12 to 19 months. Several other studies did not observe a similar beneficial effect, but these studies are short-term: 1 dose to 1 month (xx). These observations are of questionable relevance since the Swedish group suggests that benefits of therapy require about 6 months to become evident.

The issue of treating patients with dilated cardiomyopathy with beta blockers is unsettled. In patients with heart failure there is clearly the potential for catastrophic deterioration during therapy with beta blockers. However, most patients with congestive cardiomyopathy can tolerate beta blockers. The role of this therapy for patients with dilated caridomyopathy remains to be established.

Nonglycoside, noncatecholamine inotropes

The only agent available for long term treatment of myocardial systoli failure is digitalis. Because of its limitations and the problems with oral catecholamin-like drugs, the development of new agents which improve the limited contractile reserve of the heart is a high priority(44,45).

Amrinone is the prototype of the bipyridine derivatives. In isolated hearts it has a substantial inotropic effect that is not mediated by adrenergic or glycosidic mechanisms. Its principle actions may be to inhibit phosphodiesterase and increase the concentration of cyclic AMP. It is also a significant vasodilator, and its clinical effects may be predominantly due to this property. The initial studies of oral amrinone in heart failure were promising. However, it may provoke significant ventricular arrhythmias, and its gastrointestinal side-effects limit its chronic use. Two studies have shown that whil amrinone is more effective at higher doses, side effects (abdominal pain, incresed liver function studies, decreased platelets) significantly limit its chronic use. Amrinone is available in intravenous form.

Milrinone is a congener of amrinone. It is more potent than amrinone and may be better tolerated. However, its beneficial effects are lost within two months.

Sulmazol (AR-L 115) Short-term oral administration resulted in a dramatic increase in ejection fraction and cardiac index.

Fenoximone (MDL 17,043) is an imidazole derivative which als acts by inhibiting phosphodiesterase. In short- and long-term studies it has been well-tolerated and improves hemodynamics and symptoms in patients with failure.

Other approaches

Oral catecholamines have beneficial effects on short-term hemodynamics. To date, however, these agents have proven disappointing for chronic therapy of heart failure. This observation may be consistent with the view of catecholamines as toxic agents. Levodopa, coenzyme Q and taurine have also been suggested (12, 84, 190).

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