Clinical Profile of Restrictive Cardiomyopathy

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SUMMARY  The characteristic hemodynamic features of restrictive cardiomyopathy (normal or reduced cardiac index, normal ventricular systolic function, and "dip and plateau" early in diastole) are traditionally associated with pathologic evidence of inflammation, infiltration and fibrosis. Prognosis is usually poor. Nine patients with restrictive hemodynamic features were recently identified in our laboratory; six were males, three were females, and ages ranged from 23-57 years (mean 47 years). Only one was asymptomatic. Chest pain, dyspnea on exertion and fatigue were the most common symptoms. Echocardiography revealed various degrees of left ventricular wall thickening, but no significant pericardial effusion, pericardial thickening or calcification. Mean left ventricular end-diastolic pressure was 25 mm Hg, cardiac index 2.8 l/min/m² and ejection fraction 0.63. Endomyocardial and pericardial biopsies, obtained in two patients, were normal. Follow-up (mean 22 months, range 16-42 months) revealed no cardiac deaths. These findings support the hypothesis that the restrictive hemodynamic profile does not necessarily indicate the presence of a specific pathologic process in the subendocardium or myocardium and that the prognosis is not necessarily ominous. The common pathophysiologic feature for this syndrome appears to be reduced ventricular diastolic compliance, but the etiology in many cases is unclear.

CARDIOMYOPATHIES have been divided into congestive, hypertrophic and restrictive types, and a specific hemodynamic and clinical profile has been described for each class and correlated with specific etiologies.

The hemodynamic pattern of restrictive cardiomyopathy is characterized by an elevated filling pressure in the ventricles associated with normal or nearly normal systolic function. Ventricular pressure declines significantly at the onset of diastole and then rises abruptly and rapidly in early diastole. This dip-and-plateau filling pattern in the ventricular diastolic pressure tracing is manifest in the atrial pressure tracing as a prominent y descent followed by a rapid rise and plateau. The rapid rise and abrupt plateau in early diastolic ventricular pressure gives rise to the "square-root" sign. The right and left ventricular diastolic pressures may be superimposable or within 3-4 mm Hg of one another when simultaneously recorded. Thus, the hemodynamic findings may closely simulate constrictive pericarditis.

The restrictive physiology has been attributed to reduced diastolic ventricular compliance, presumably resulting from fibrotic or infiltrative processes involving the subendocardium and/or myocardium. Specific etiologies have been reported to include amyloidosis, sarcoidosis, hemochromatosis, Loeffler's eosinophilic endomyocardial disease and endomyocardial fibrosis. Except for hemochromatosis, these conditions have no known specific therapy and are associated with progressive deterioration and a grave prognosis.

In contrast, we have found that restrictive cardiomyopathy usually has a stable course, a relatively good prognosis, and no specific etiology. This report describes our experience with restrictive cardiomyopathy at the Peter Bent Brigham Hospital over a 3-year period and correlates clinical, hemodynamic and pathologic findings.

Methods

Between July 1, 1975 and December 31, 1978, approximately 2000 diagnostic catheterizations were performed at the Peter Bent Brigham Hospital. Patients with left- or right-heart catheterization only or those without high-quality recordings of both right and left ventricular pressures were excluded. Records of the remaining 1200 patients were reviewed and those with the following hemodynamic findings, consistent with restrictive cardiomyopathy, were selected: 1) elevation in both left ventricular end-diastolic pressure (LVEDP) and right ventricular end-diastolic pressure (RVEDP) (normal LVEDP < 12 mm Hg and RVEDP < 8 mm) not explicable by valvular, coronary, pericardial or congenital heart disease; 2) normal left ventricular systolic function (ejection fraction > 50%); and 3) characteristic early diastolic dip and subsequent rapid plateau in both ventricular pressure curves with abnormal elevation in ventricular pressure achieved with the rapid filling wave.

Patients or their physicians were contacted to assess clinical status, New York Heart Association classification and therapeutic program. The clinical presentation, noninvasive studies, catheterization data and follow-up information on patients with the diagnosis of restrictive cardiomyopathy according to the above hemodynamic criteria are the basis of this report.

Results

Clinical Characteristics

Nine of 79 patients with the diagnosis of cardiomyopathy met the criteria for diagnosis of restrictive cardiomyopathy and were selected for review. Table 1 summarizes the clinical presentation and noninvasive data. There were six males and three females.
Mean age at the time of presentation was 47 years (range 23–57 years). Patients presented with a variety of complaints that were related to the cardiovascular system. These included dyspnea on exertion and fatigue (five patients), peripheral edema (three patients), angina (one patient) and atypical chest pain (three patients). In these patients, the pain was not consistently related to exertion nor was a substernal location and was more a stabbing than pressure sensation. One patient presented with new atrial arrhythmias. Two patients had associated chronic obstructive lung disease and one had von Recklinghausen’s syndrome. One asymptomatic patient was studied because he had a diagnosis of Noonan’s syndrome, evidence of a hypertrophic cardiomyopathy, and required complete cardiovascular evaluation before he underwent general anesthesia. In summary, five patients had symptoms of dyspnea or congestive heart failure, four had chest pain and one was asymptomatic.

At the time of presentation, these patients were receiving a variety of cardiovascular medications. Five were taking digoxin and diuretics (including furosemide and spironolactone), four were taking various nitrate preparations and two were taking β-blocking agents. Two patients were on no medications.

Physical findings were variable. One patient had an apical holosystolic murmur, one patient had a holosystolic murmur at the lower left sternal border, five patients had ejection systolic murmurs, two had third heart sounds, and one patient had a fourth heart sound. Three patients had evidence of systemic venous congestion with jugular venous distension. Three patients had peripheral edema; one of these patients also had ascites. Two patients were in atrial fibrillation, which was well controlled on digoxin therapy, and seven patients were in sinus rhythm.

**Electrocardiogram**

A variety of electrocardiographic findings were present that were consistent with enlargement or hypertrophy of one or more cardiac chambers. One patient had left ventricular hypertrophy with associated ST-T-wave changes consistent with digoxin
therapy or a "strain" pattern. Two patients demonstrated electrocardiographic evidence of isolated right ventricular hypertrophy and one patient demonstrated biventricular hypertrophy. Two patients had nonspecific abnormalities of the ST segments and T waves and three had normal ECGs except for the presence of occasional atrial premature contractions in one of the three.

Chest X-ray

The roentgenographic examination revealed a variety of pulmonary and cardiomegaly abnormalities. Five patients had cardiomegaly (cardiothoracic ratio > 0.50), though the specific chambers that were enlarged could not be determined in two of these patients. One patient demonstrated left ventricular enlargement and two showed biventricular enlargement. Two patients demonstrated pulmonary vascular redistribution, and one patient had prominence of the pulmonary artery.

Echocardiography

Echocardiographic findings in these patients were variable. One patient demonstrated asymmetric septal thickening and one showed abnormal systolic motion of the anterior mitral leaflet, but had no evidence of resting or provokable outflow tract obstruction by echocardiographic examination or systolic time interval analysis. Two patients demonstrated left ventricular wall thickening, one showed left ventricular enlargement and two had right ventricular enlargement. One patient had left atrial enlargement. The echocardiogram was completely normal in two patients. In summary, echocardiograms demonstrated varying degrees of left ventricular wall thickening, left and/or right ventricular enlargement, but no significant thickening or calcification of the pericardium or effusion.

Cardiac Catheterization

All patients underwent diagnostic biventricular catheterization and left ventriculography. Coronary arteriography was performed in eight patients. The hemodynamic and angiographic findings are summarized in table 2. The cardiac index was normal in four patients (> 2.8 l/min/m²) and depressed in the other five patients, including one with an index of 1.71/min/m². Four patients had systolic arterial

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hypertension (systolic aortic pressure ≥ 150 mm Hg), but it was mild (< 170 mm Hg) in each case. Left and right ventricular end-diastolic pressures were elevated in all patients, with a group mean ± SD of 25 ± 6 mm Hg and 16 ± 5 mm Hg, respectively. All patients had a prominent dip and rapid plateau in the left and right ventricular pressure tracings during diastole (fig. 1). There was a corresponding prominent y descent in the pulmonary capillary wedge and right atrial pressure tracings (fig. 2). In all but patients 3 and 5, the left
ventricular end-diastolic pressure exceeded the right ventricular end-diastolic pressure by at least 5 mm Hg. The mean pulmonary capillary wedge pressure was elevated in all patients (20 ± 6 mm Hg), consistent with the patients' complaints of dyspnea. The mean right atrial pressure was elevated in eight patients (14 ± 4 mm Hg), thereby explaining the symptoms and signs of systemic congestion. Pulmonary and systemic vascular resistances were varied from patient to patient, and no consistent pattern was evident.

Figure 1 shows the simultaneous right and left ventricular pressure recordings for patient 6. It demonstrates the characteristic early diastolic dip and rapid plateau in ventricular pressures that are characteristic of restrictive cardiomyopathy or constrictive pericarditis. The near-equality of these right- and left-sided pressures in diastole is also demonstrated in figure 2. In the patient shown, diastolic pressures remained nearly equal during leg raising and supine exercise, maneuvers that have been reported to cause a disproportionate elevation in left ventricular end-diastolic pressure in patients with restrictive cardiomyopathy. Because ventricular diastolic pressures were nearly equal — except at end-diastole — and left ventricular end-diastolic pressure could not be selectively elevated by any hemodynamic maneuver, the question of a pericardial constrictive process was raised in this patient. Right ventricular endomyocardial biopsy was obtained. The myocardium, stained with hematoxylin and eosin, Congo red and Prussian blue, was normal; there was no evidence of amyloid or iron deposition. The patient subsequently underwent thoracotomy for insertion of an epicardial pacemaker (to treat her atrial bradyarrhythmias), at which time pericardial biopsy was obtained. The pericardium demonstrated no thickening or fibrosis. This differential diagnosis — restrictive cardiomyopathy vs constrictive pericarditis — also was raised in patients 3 and 5, whose left and right ventricular end-diastolic pressures were within 3-4 mm Hg of each other.

Patient 3 underwent a right ventricular endomyocardial biopsy at the time of catheterization and an open pericardial biopsy a few days later. The pericardium was normal and the myocardium, studied by similar histochemical techniques, was also free of infiltrative processes. Patient 5 had a history of alcohol abuse, Laennec's cirrhosis and biventricular congestive heart failure. At catheterization, the hemodynamic findings were consistent with restrictive cardiomyopathy or constrictive pericarditis. Further diagnostic procedures were not undertaken because of the severity of hepatic decompensation. He died 1 month after catheterization. A postmortem examination was not performed.

Ventriculography revealed a normal ejection fraction (range 0.52–0.76) in all patients. Four patients had evidence of an increase in left ventricular free wall thickness, two had mild left ventricular enlargement, one had anteroapical hypokinesis and one patient had mild mitral regurgitation. Wall motion, wall thick-

ness, aortic valve mobility and mitral valve coaptation were normal in the rest of the group.

Follow-up

Available follow-up information for this group with restrictive cardiomyopathy is presented in table 3. Most demonstrated clinical improvement. Patient 5 died of hepatic failure secondary to Laennc's cirrhosis 1 month after catheterization. Patient 2 was lost to follow-up. The remaining patients are alive at a mean follow-up interval of 22 months (range 16-42 months). Six patients have improved by at least one New York Heart Association classification, and two are unchanged. Predominant symptoms, New York Heart Association functional status, and medical regimen at follow-up are summarized in table 3.

Discussion

Restrictive cardiomyopathy reportedly results from a variety of pathologic processes that may involve the myocardium or endocardium. This hemodynamic profile can result from amyloidosis, hemochromatosis, glycogen deposition, and fibrosis from a number of diverse etiologies. These processes reduce ventricular diastolic compliance and restrict inflow of blood. Stroke volume is accommodated by the stiffened ventricle only through an abnormal rise in diastolic pressure, which accounts for the congestive symptoms as well as the characteristic hemodynamic signs.

In some cases of restrictive cardiomyopathy, a specific infiltrative process such as amyloidosis can be identified. In the few cases that have been reported, the prognosis has been uniformly poor. In other instances, this clinical and hemodynamic profile may be

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Abbreviations: AF = atrial fibrillation; DOE = dyspnea on exertion; CP = chest pain.
associated only with nonspecific ventricular hypertrophy and/or fibrosis.\textsuperscript{7} Can certain patients with con- gestive cardiomyopathy develop restrictive physiology when myocardial fibrosis becomes sufficient to reduce diastolic compliance? Our study suggests that evolution from congestive to restrictive cardiomyopathy is unlikely because all of our patients demonstrated preservation of ventricular systolic function (e.g., left ventricular ejection fraction 52–76\%) at a time when there was a clear abnormality in both right and left ventricular filling pressures indicative of restrictive physiology.

In our series, patients with restrictive cardiomyopathy presented with symptoms of left and/or right ventricular failure, chest pain in the absence of significant narrowing of any epicardial coronary artery and/or symptoms from atrial arrhythmias. Physical findings were nonspecific, and evidence of systemic venous congestion was present in fewer than half the cases. Electrocardiographic findings, though nonspecific, may be compatible with restrictive myopathic process if evidence of left and/or right ventricular hypertrophy with or without a strain pattern is present. The echocardiogram is helpful in ruling out thickening or calcification within the pericardium or the presence of pericardial fluid, and may suggest a restrictive myopathic process if there is evidence of left and/or right ventricular wall thickening or asymmetric septal thickening. In no patient in our series was any pattern of abnormal ventricular diastolic wall motion suggestive of restrictive cardiomyopathy observed on the echocardiogram.

Patients with restrictive cardiomyopathy require biventricular catheterization with thorough hemodynamic evaluation to differentiate this condition from the more common causes of chest pain, congestive heart failure or arrhythmias. Coronary arteriography will establish or rule out the presence of epicardial coronary artery disease. However, a careful, more complete hemodynamic evaluation is required to identify more obscure cardiac causes of chest pain, such as pulmonary hypertension or restrictive cardiomyopathy.

A normal endomyocardial biopsy does not rule out the presence of restrictive cardiomyopathy, as illustrated by patients 3 and 6. Despite hemodynamic findings that were typical for restrictive cardiomyopathy, including similarity of right ventricular and left ventricular end-diastolic pressures in patient 3, they both had normal endomyocardial biopsies. Thus, at times, pericardial exploration with biopsy may be required to differentiate between restrictive cardiomyopathy and constrictive pericarditis. In general, however, patients with restrictive physiology have dissimilar left and right ventricular end-diastolic pressures. Furthermore, cardiac murmurs are also uncommon in constrictive disease.

It is probable that when restrictive cardiomyopathy is associated with a specific infiltrative or fibrotic process, it carries a poor prognosis.\textsuperscript{6,7} However, in our series, in which no specific etiology for the restrictive hemodynamic profile could be identified, several patients noted significant symptomatic improvement over the follow-up interval. This suggests that in patients with restrictive cardiomyopathy, endomyocardial biopsy may be of prognostic importance.

We could not identify the etiologic agents and pathologic processes that resulted in the restrictive hemodynamic profile in our patients and can only speculate on the causes of this condition. In view of the somewhat reversible nature of the process, as suggested by the clinical improvement, the initial presentation and hemodynamic pattern may have resulted from myocardial edema and/or scattered inflammatory cell infiltration resulting from a subacute infectious or toxic etiology. Myocarditis has been shown experimentally to cause reduction in ventricular diastolic compliance and cause elevation in filling pressures and atrial distention.\textsuperscript{8} There may also be a subtle increase in the total cardiac volume contained within the confines of the as yet unyielding non-compliant pericardial sac. Such hemodynamic alterations may precipitate symptoms of pulmonary and systemic venous congestion, and if there is epicarditis as well, there may be atrial arrhythmias and/or chest pain. Conversely, with resolution of the subtle inflammatory changes, diastolic compliance increases, atrial distention is relieved, pericardial tension slackens and symptoms improve or resolve completely.

Possible alterations in diastolic cardiac tone or myocardial relaxation should also be considered. The similarity of hemodynamic findings in hypertrophic and restrictive cardiomyopathies are of interest in this regard. Slow-calcium-channel blockers such as verapamil have alleviated symptoms in patients with hypertrophic obstructive cardiomyopathy, presumably by reducing diastolic ventricular tone and increasing compliance.\textsuperscript{9} Such agents might be of some therapeutic benefit in patients with restrictive cardiomyopathy in whom no specific infiltrative process can be identified by histologic examination. Such a study, though important, would be difficult to perform because restrictive cardiomyopathy is infrequent, its clinical presentation nonspecific, and biventricular catheterization with careful hemodynamic evaluation is required for diagnosis.

References

Beneficial Effects of Afterload Reduction Therapy in Patients with Congestive Heart Failure and Moderate Aortic Stenosis

BARRY H. GREENBERG, M.D., AND BARRY M. MASSIE, M.D.

SUMMARY Patients with congestive heart failure have improved cardiac performance when afterload is reduced by drugs that lower systemic vascular resistance. However, in the presence of mild-to-moderate aortic stenosis, the response to such drugs is uncertain because the major impedance to left ventricular emptying may occur at the level of the aortic valve. To determine whether vasodilator therapy is useful in this setting, we evaluated the response to afterload reduction in 11 patients with severe congestive heart failure and reduced aortic valve area.

All patients underwent catheterization to document the severity of stenosis before study. Reduced valve area was due to native valve stenosis in three patients and to the presence of aortic prostheses in eight patients. A transvalvular gradient was measured in all patients. The peak gradient was 17 ± 3 mm Hg (mean ± SEM), and the aortic valve area index was 0.7 ± 0.1 cm²/m².

After optimal doses of either hydralazine (nine patients) or prazosin (two patients), cardiac index increased from 2.2 ± 0.1 to 3.3 ± 0.2 l/min/m² (p < 0.001) and stroke volume index increased from 28 ± 2 to 38 ± 2 ml/m² (p < 0.001). Systemic vascular resistance fell from 1649 ± 94 to 1061 ± 68 dyn-sec-cm⁻⁵ (p < 0.001), and mean arterial pressure decreased from 93 ± 4 to 88 ± 4 mm Hg (p < 0.01). Hemodynamics were improved in all 11 patients regardless of valve area.

We conclude that patients with heart failure and mild-to-moderate aortic stenosis respond favorably to drugs that lower systemic vascular resistance. In such patients, resistance to ventricular emptying is determined predominantly by systemic vascular resistance rather than by aortic valve area.

A COMPENSATORY INCREASE in systemic vascular resistance frequently occurs in response to low cardiac output in patients with congestive heart failure. Recently, the potentially deleterious effect of increased afterload in patients with left ventricular dysfunction has been appreciated. Afterload reduction, using drugs that lower systemic vascular resistance, facilitates emptying of the impaired left ventricle and frequently results in improved cardiac performance and symptomatic improvement in such patients.

Patients with congestive heart failure may also have aortic stenosis that is not sufficiently severe to indicate valve replacement. Reduced aortic valve area may be due to disease of the native valve or to the presence of an aortic prosthesis. In such cases, the response to afterload reduction therapy is uncertain because resistance at the level of the aortic valve may contribute substantially to left ventricular afterload. If this were true, drugs that lower systemic vascular resistance would be expected to have little beneficial effect on cardiac performance and might be harmful.

To determine whether afterload reduction therapy is beneficial in patients with reduced aortic valve area, we evaluated the response of a group of patients with severe congestive heart failure and mild-to-moderate aortic stenosis to hydralazine, or prazosin, drugs whose predominant effect is to reduce systemic vascular resistance.

Methods

Patient Population

Eleven patients with severe congestive heart failure and reduced aortic valve area were evaluated. Their clinical and hemodynamic profile is shown in table 1. There were nine males and two females whose mean age was 59 ± 3 years (SEM). Three patients had native valve stenosis and eight had an aortic valve prosthesis.
Clinical profile of restrictive cardiomyopathy.
J R Benotti, W Grossman and P F Cohn

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