Restrictive cardiomyopathy versus constrictive pericarditis: role of endomyocardial biopsy in avoiding unnecessary thoracotomy

MARK H. SCHOFIELD, M.D.,* EDWARD W. SUPPLE, M.D.,** G. WILLIAM DEC, JR., M.D., JOHN T. FALLON, M.D., PH.D., AND IGOR F. PALACIOS, M.D.

ABSTRACT Despite careful clinical, noninvasive, and hemodynamic assessment of patients with constrictive/restrictive physiology, the differentiation of restrictive cardiomyopathy from constrictive pericarditis remains difficult. We examined the role of right ventricular endomyocardial biopsy in defining the underlying process in 54 patients with evidence of constrictive/restrictive physiology, including 38 patients with profound symptoms of heart failure in whom diagnostic/therapeutic thoracotomy was contemplated (group I) and 16 patients with milder symptoms (group II). All patients in group I had NYHA class III or IV heart failure with depressed cardiac index (mean 2.5 liters/min/m²), right atrial hypertension (mean 15 mm Hg), and normal left ventricular ejection fraction (mean 59%). Endomyocardial biopsy identified a specific source of restrictive cardiomyopathy in 15 of 38 patients (39%) (11 amyloid, four myocarditis). Of the 23 remaining patients with either normal biopsy findings or nonspecific abnormalities on biopsy, 18 had intraoperative or autopsy evaluation of their pericardium, and constriction was found in 14 (77%). A specific form of restrictive cardiomyopathy was also identified in four of the 16 patients with milder symptoms (group II). We conclude that endomyocardial biopsy is useful in patients with severe constrictive/restrictive physiology. It identifies a large subset of patients with specific forms of restrictive cardiomyopathy in whom thoracotomy should be avoided. It supports the need for thoracotomy and the likelihood of finding pericardial constriction in patients without specific pathologic findings.


THE DIFFERENTIATION of restrictive cardiomyopathy from constrictive pericarditis remains one of the major diagnostic dilemmas encountered in clinical cardiology. For patients with symptoms of heart failure in whom these diagnoses are considered, the distinction of these two conditions is critical, since both their management and ultimate prognoses are quite different. Similarities in clinical presentation between these two conditions have long been recognized and efforts to separate them on the basis of noninvasive methods or angiographic/hemodynamic characteristics have been fraught with difficulty. Exploratory thoracotomy for pericardial evaluation, with its attendant risks, remains the definitive technique for establishing a diagnosis in many patients.

Transvenous endomyocardial biopsy has been used increasingly to diagnose myocardial disease in patients presenting with symptoms of heart failure of undetermined etiology. The purpose of this study was to examine the role of right ventricular endomyocardial biopsy in defining the need for exploratory thoracotomy in patients with symptomatic heart failure due to constrictive/restrictive physiology.

Methods

Inclusion criteria. Between January 1, 1975, and March 31, 1985, 54 patients with symptoms of heart failure underwent right ventricular endomyocardial biopsy after demonstrating constrictive/restrictive physiology during cardiac catheterization. The criteria for constrictive/restrictive physiology used in this study were: (1) left ventricular ejection fraction of at least 40% by radionuclide and/or contrast angiography, (2) equalization of diastolic pressures within 5 mm Hg, (3) a prominent "Y" descent in the right atrial recording, (4) a "dip and plateau" pattern in the right ventricular pressure tracing, (5) absence of left ventricular hypertrophy on the electrocardiogram, and (6)
when right atrial angiography was performed, a ventricular filling pattern suggestive of rapid filling and early diastolic plateau (with or without straightening of right heart border or poor pulsations sometimes seen in constriction).

All patients included in this study gave a complete history and underwent physical examination, chest roentgenogram, and electrocardiogram. In addition, most of these patients had further cardiac noninvasive evaluation by echocardiography and radionuclide-gated blood pool scan to evaluate cardiac size and function. Pericardial thickening was defined echocardiographically by the presence of a band of dense echoes emanating from the space outside the epicardium with the same direction and amplitude of motion as the epicardium. All patients underwent right heart catheterization and determination of cardiac output. Left heart catheterization and coronary angiography were performed in all patients older than 40 years and/or with suspected coronary artery and/or valvular heart disease to exclude coronary narrowing or valvular abnormalities as a cause of cardiac dysfunction. In each case, the clinician caring for the patient had requested that right heart catheterization and biopsy be performed for diagnostic purposes; thus the time of biopsy relative to the duration of symptoms was determined only by the timing of the referral.

On the basis of clinical presentation and catheterization findings, the patient population was subdivided into two groups for the purpose of subsequent clinical evaluation. Group I consisted of 38 patients with profound symptoms of heart failure who met the criteria for a severe constrictive/restrictive syndrome worthy of surgical consideration, i.e., diagnostic/therapeutic thoracotomy with pericardial stripping. These criteria were (1) NYHA class IV heart failure or (2) NYHA class III heart failure with right atrial pressure of at least 10 mm Hg and/or cardiac index of 2.4 liters/min/m² or less. Group II consisted of 16 patients with milder clinical presentations.

Transvenous endomyocardial biopsy and histologic technique. At the end of cardiac catheterization, right ventricular endomyocardial biopsy was performed according to a technique described previously.20-22 A Cave's-Schulz-Stanford bioprome was inserted through the right internal jugular vein to obtain multiple biopsy specimens, each measuring 1 to 3 mm in diameter, from the right ventricle. Three to five biopsy fragments were fixed by immersion in buffered 10% formalin for routine histologic studies; one fragment was placed in 2.5% buffered glutaraldehyde for potential electron microscopy study; and one sample was snap frozen for immunochemical studies. Stains of paraffin sections were made with hematoxylin and eosin, Masson trichrome, and Congo red. The frozen endomyocardial tissue was sectioned and stained with hematoxylin and eosin and toluidine blue. The fragment for electron microscopy was embedded in plastic, and 1 μm sections were cut and stained with toluidine blue for light microscopic examination.

Pathologic evaluation. The biopsy specimens were classified on the basis of a review of all light microscopic slides, including plastic thick sections and frozen tissue slides. Criteria used to make specific pathologic diagnoses were as follows.

Myocarditis. We classified biopsy specimens as positive for myocarditis whenever there was histologic evidence of an interstitial inflammatory infiltrate associated with necrotic or degenerative myocytes with or without interstitial fibrosis.23

Amyloid deposition. Amyloid deposition was diagnosed by a positive Congo red stain with typical green birefringence under polarized light with subsequent confirmation by a positive thioflavine-T1 stain and electron microscopy.

Endomyocardial fibrosis. Changes of endomyocardial fibrosis were diagnosed in the presence of thickening and fibrosis of endocardium extending into subjacent myocardium.

Changes consistent with radiation damage. These changes included myocyte hypertrophy and vacuolar degeneration, marked interstitial fibrosis, endocardial fibrosis, and atypical interstitial fibroblasts and endothelial cells.

Non-specific changes. Abnormal but nondiagnostic changes included interstitial or focal replacement fibrosis, myocyte hypertrophy, or mild focal fibrous thickening of the endocardium.

No diagnostic abnormality. These endomyocardial specimens were considered to be entirely normal.

Clinical evaluation. Patients were followed for a mean period of 21 months (range 1 to 91) after their biopsy. Sixteen patients underwent subsequent thoracotomy, including 15 of the highly symptomatic patients from group I. One patient from group II underwent thoracotomy for reasons other than constrictive/restrictive syndrome (surgical ablation of her atrioventricular node). Of 18 patients who died during the follow-up period, conventional postmortem examinations were performed in three, and the pathologic findings of the transvenous endomyocardial biopsy were compared with postmortem results.

Statistical methods. Univariate statistical methods were used to screen those hemodynamic features potentially useful in differentiating patients in whom a definitive diagnosis of pericardial constriction or restrictive cardiomyopathy was ultimately made. Multivariate methods, logistic regression analysis, and the Cox model of proportional hazard with the Breslow modification were applied to those variables determined to have at least marginal (p < .10) predictive value from the univariate analyses. In this manner, an attempt was made to identify significant (p < .05) independent variables predictive of either diagnosis.24,25

Results

Clinical, echocardiographic, and hemodynamic profiles. Of the 54 patients in this study, there were 32 men and 22 women. Their ages ranged from 22 to 89 years (mean 51). Thirty-four of the 38 patients in group I had NYHA class IV heart failure symptoms. Six patients had had prior exposure to mediastinal irradiation, five had a history of tuberculosis, and four had had prior cardiac surgery. Twelve patients in group I had evidence of pulmonary congestion with rales. This included five patients later shown to have cardiac amyloidosis. Of four other patients with rales who underwent pericardial evaluation, one patient was shown to have idiopathic restriction and three patients had pericardial constriction (including two with pancearditis).

Echocardiography was performed in 39 patients. Pericardial thickening was observed in nine, including four patients ultimately found to have constriction; two patients with pericardial thickening on echocardiography were found to have no constriction intraoperatively. Three patients with pericardial thickening on echocardiography did not undergo pericardial evaluation. Conversely, five patients were found to have normal pericardial thickness by echocardiography examination but subsequently demonstrated constriction at the time of pericardial evaluation.

The resting hemodynamic findings of patients with
the severe constrictive/restrictive syndrome (group I) and the milder syndrome (group II) are given in table 1.

Diagnoses from transvenous endomyocardial biopsy and subsequent pericardial evaluation

Group I. Of 38 patients with the severe constrictive/restrictive syndrome, a diagnosis of cardiac amyloidosis was made in 11. Characteristic infiltrates and foci of myocarditis were observed in four additional patients. Thus biopsy identified a specific form of restrictive cardiomyopathy in 39% of patients (15/38). In one patient with a history of irradiation, changes consistent with myocardial radiation damage were observed. The biopsy was abnormal, showing nonspecific changes, in 19 patients and entirely normal in three patients.

As shown in figure 1, subsequent pericardial evaluation was performed in 18 of the patients with normal or nonspecific biopsy results (15 by thoracotomy and three at postmortem examination). Pericardial thickening and constriction was evident in 14 of these patients. This included six of 10 patients undergoing thoracotomy with nonspecific changes on biopsy and all three patients undergoing thoracotomy with a normal biopsy. The patient whose biopsy was consistent with radiation damage was found to have pericardial constriction at the time of thoracotomy. Another patient whose biopsy demonstrated myocarditis underwent thoracotomy because of persistent symptoms despite medical treatment and was found to have pericardial constriction additionally. Two additional patients with nonspecific changes on the biopsy were subsequently found to have pericardial thickening at postmortem examination, as did one of the patients with myocarditis.

The definitive diagnosis of restriction was made either by the presence of a specific form of restrictive cardiomyopathy on biopsy or by the absence of constriction at the time of pericardial evaluation. When the hemodynamic findings of patients with this diagnosis were compared with those of patients ultimately found to have constriction, no significant differences and no independently predictive differentiators were identified (table 2).

Group II. Of 16 patients with the milder constrictive/restrictive syndrome, a specific form of restrictive cardiomyopathy was observed in the biopsy specimens

TABLE 1

<table>
<thead>
<tr>
<th>Hemodynamic findings in the constrictive/restrictive syndrome</th>
<th>Group I (severe syndrome)</th>
<th>Group II (mild syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (mm Hg)</td>
<td>15 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>19 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>PA systolic (mm Hg)</td>
<td>42 ± 2</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>PA diastolic (mm Hg)</td>
<td>20 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.5 ± 0.1</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 2</td>
<td>62 ± 2</td>
</tr>
</tbody>
</table>

RA = right atrial pressure; PCW = pulmonary capillary wedge pressure; PA = pulmonary arterial; LVEF = left ventricular ejection fraction.

FIGURE 1. Pathologic diagnosis by right ventricular endomyocardial biopsy in 38 patients with severe constrictive/restrictive syndrome (group I). The presence of constriction at the time of pericardial evaluation in 18 of these patients is also shown. NSC = nonspecific changes.

| TABLE 2 |
|---------------------------------|-----------------|-----------------|
|                                    | Constriction  | Restriction     |
|                                    | (n = 12)       | (n = 19)        |
| RA (mm Hg)                       | 16 ± 1         | 14 ± 2          |
| PCW (mm Hg)                      | 19 ± 1         | 20 ± 1          |
| PA systolic (mm Hg)              | 40 ± 5         | 41 ± 3          |
| PA diastolic (mm Hg)             | 19 ± 2         | 20 ± 2          |
| Cardiac index (l/min/m²)         | 2.2 ± 0.2      | 2.5 ± 0.2       |
| LVEF (%)                         | 58 ± 3         | 59 ± 2          |

Abbreviations as in table 1.

*For the purpose of this comparison, the two patients with both myocarditis and pericardial constriction were placed in the restriction column.
of four (25%), including amyloidosis in one patient, endomyocardial fibrosis in two patients, and myocarditis in one patient. Nonspecific changes were observed in six patients. The biopsy was normal in six patients.

One patient in this group with myocyte hypertrophy on biopsy underwent cardiac surgery for ablation of her atrioventricular node and no pericardial constriction was observed at that time.

Subsequent clinical follow-up. Eighteen deaths occurred during the follow-up period, all in patients with the severe constrictive/restrictive syndrome. Death occurred in seven of the 12 patients with cardiac amyloidosis, one suddenly and six due to progressive heart failure. The mean duration between biopsy diagnosis of amyloidosis and death was 6 months. There were six deaths in the group of patients ultimately found to have pericardial constriction. In two of these the diagnosis of constriction was made at the time of autopsy. Of the four remaining cases, one death occurred in the setting of low cardiac output postoperatively, two deaths occurred from other postoperative complications, and one death occurred 1 year after pericardial stripping with recurrent pleuropericardial effusions.

Of the remaining five deaths, one occurred in a patient whose biopsy revealed myocarditis and whose autopsy revealed pancarditis with constriction. Another patient died from heart failure 31 months after biopsy; this patient had had a biopsy with nonspecific changes and a normal pericardium at the time of thoracotomy and is therefore believed to have had idiopathic restrictive cardiomyopathy. Three deaths occurred in patients whose biopsies revealed nondiagnostic abnormalities but in whom further pericardial evaluation was not undertaken.

Discussion

Our results indicate the importance of transvenous endomyocardial biopsy in patients with constrictive/restrictive physiology, particularly in patients with severe symptoms in whom diagnostic/therapeutic thoracotomy is contemplated. The risk of such surgery in patients with restrictive cardiomyopathy is appreciable, and deaths occurring shortly after exploratory thoracotomy in patients shown to have cardiac amyloidosis, in particular, have been well documented.5,18 Endomyocardial biopsy established the diagnosis of a specific form of restrictive cardiomyopathy in 39% (15/38) of patients with the severe syndrome in our series, thereby obviating the need for thoracotomy in all but one of these patients.

The preoperative differentiation of pericardial constriction from cardiac restriction has been associated with a significant diagnostic error rate.17 Certain features of the clinical presentation may suggest a greater likelihood of one or the other diagnosis. For example, a history of previous tuberculosis or mediastinal irradiation might lead one to consider pericardial constriction.26 However, tuberculous pericarditis has become rare, and mediastinal irradiation has been shown to affect the heart in a variety of ways, including pericardial constriction and cardiomyopathy, either alone or in combination.17,27,28 In fact, the majority of patients with either restriction or constriction have no suggestive history.26,29,30 In our series, a history of tuberculosis was present in five patients, two of whom were found to have had cardiac amyloidosis, and only one was found to have constriction at the time of pericardial exploration. Six patients in our series had a history of mediastinal irradiation, including three shown to have pericardial constriction and one without evidence of constriction at the time of pericardial evaluation. Similarly, although evidence on physical examination for pulmonary congestion may suggest a diagnosis of restriction (five of our patients with cardiac amyloidosis, one patient with idiopathic restrictive cardiomyopathy), the presence of rales does not absolutely exclude constriction, which was present in three of our patients (two with pancarditis).

Noninvasive methods such as echocardiography and nuclear magnetic resonance also have been used to attempt differentiation of myocardial restriction from constriction in certain patients.10-13 These approaches, although promising, remain to be further evaluated and the methods, in some cases, have not been validated against the gold standard of actual pericardial evaluation either by thoracotomy or autopsy. Echocardiography was not distinctly helpful in establishing a diagnosis in our series even in patients studied more recently. Echocardiographic interpretation of pericardial thickening is highly subject to gain-dependence and may lead to a false impression of pericardial fibrosis or adhesion in up to one-fourth of patients ultimately undergoing evaluation with surgery or autopsy.31 Other techniques that may have been helpful, such as computerized tomography or magnetic resonance imaging, were not used routinely in this series of patients.

Our patient population, as defined previously, is noteworthy for its systolic "competence" (mean left ventricular ejection fraction of 59%), with no significant difference in the restriction and constriction subgroups. As such, the essentially diastolic nature of these two conditions may be appreciated. Recent stud-
ies suggest that a differentiation of constrictive pericarditis and restrictive cardiomyopathy may be made by quantification of several diastolic variables, including maximal thinning rate of the left ventricular posterior wall (slower in restriction), minimal dimension to peak filling interval (prolonged in restriction), the major filling period (prolonged in restriction), and maximal filling rate (decreased in restriction). However, study of left ventricular filling is limited by intraobserver and interobserver variability and by the difficulty in normalizing values for differences in ventricular size. In addition, both heart rate changes and differences in fractional shortening may alter peak filling rate. Although the profile of early diastolic filling can be assessed with high quality M mode echocardiography, regional differences in segmental wall thickening and excursion as well as their rates of changes are important limitations to the use of this technique. Finally, there may be considerable overlap in peak filling rate data among normal patients, patients with restrictive cardiomyopathy, and patients with pericardial constriction. This precludes the use of such data as the definitive method for differentiating restriction from constriction in many patients.

Several hemodynamic criteria have been proposed to help distinguish pericardial constriction from restrictive cardiomyopathy. These include a right ventricular end-diastolic pressure to right ventricular systolic pressure ratio greater than one third or a right ventricular systolic pressure less than or equal to 40 mm Hg. Such indexes were not found to be of diagnostic use in the present series. Hemodynamic challenges, such as rapid volume loading, leg elevation, or exercise, to effect a disproportionate rise in the left ventricular diastolic pressure have been thought to be useful in identifying restrictive cardiomyopathy. Since such challenges were not generally applied to the patients in our series, we can make no comments on their usefulness.

Transvenous endomyocardial biopsy revealed an important incidence of specific forms of restrictive cardiomyopathy in the severely symptomatic group of patients in our series. Conversely, it is also of note that all three patients with normal biopsies were found to have pericardial constriction. Characterization of the pericardium by thoracotomy or autopsy was not available in seven of the patients with nonspecific biopsy changes. Nonetheless, in more than half of the patients who did undergo pericardial evaluation, constriction was observed. We therefore would advise that patients with either normal endomyocardial biopsies or nondiagnostic abnormalities on biopsy undergo exploratory thoracotomy if further treatment of a clinically severe syndrome is desired, since the likelihood of finding pericardial constriction in such patients is high. Four patients in our series with nondiagnostic changes in endomyocardial biopsy who underwent pericardial evaluation were subsequently diagnosed as having idiopathic restrictive cardiomyopathy. Thus the absence of specific forms of restrictive cardiomyopathy on biopsy does not unequivocally indicate constriction, as demonstrated also by Benotti et al. A small subset of patients with the severe syndrome were found to have myocarditis at the time of biopsy. Although this process may have resulted in myocardial restriction, it is noteworthy that two of these patients were subsequently found to have pericardial constriction as well, indicative of a pancarditis. Therefore the clinical approach in such patients may be dictated by whether the clinical syndrome is primarily governed by myocarditis or pericardial constriction. If myocarditis does not respond to medical therapy, as was the case in one of our patients, exploratory thoracotomy may then be of diagnostic and therapeutic benefit. The coexistence of pericardial constriction with myocarditis, postradiation cardiomyopathy, or other forms of cardiomyopathy has also been observed in a subset of patients reported by Seifert et al. These workers reported, however, that the outcome of patients with constrictive pericarditis and restrictive cardiomyopathy was no better than those with restrictive cardiomyopathy alone and were hesitant to recommend pericardial stripping in such patients, particularly the postradiation subgroup.

The utility of transvenous endomyocardial biopsy in patients with more moderate symptoms and constrictive/restrictive physiology is less clear. Such patients usually do not require surgical intervention. Nonetheless, one-fourth of the patients in group II of our series were found to have a diagnostic abnormality on biopsy that proved useful in guiding subsequent management. Further prospective work will be required to clarify the role of biopsy in this group of patients with abnormal physiology but mild-to-moderate symptoms.

We conclude that endomyocardial biopsy is essential in the evaluation of patients with the severe constrictive/restrictive syndrome in whom exploratory thoracotomy is being considered. It identifies a large subset of patients with specific forms of restrictive cardiomyopathy in whom thoracotomy should be avoided. It also supports the need for thoracotomy and the likelihood of finding pericardial constriction in patients without pathologic changes specific for infiltrative forms of restrictive cardiomyopathy.
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