Clinical features of mixed physiology of constriction and restriction: Echocardiographic characteristics and clinical outcome

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Abstract  Aims: An entity of patients with mixed physiology of constriction and restriction has been reported, however, the characteristics of these patients have not been well documented. We evaluated the clinical features and the outcome of these patients.

Methods and results: Study subjects consisted of 38 patients (57 ± 14 years, 8 females, 30 males) who were diagnosed as having mixed physiology based on transthoracic and/or transesophageal echocardiography, MRI (or CT), cardiac catheterization, endomyocardial biopsy and/or surgical findings. Prior radiation therapy was the most frequent (50%) cause of mixed physiology followed by coronary artery bypass graft without prior radiation (24%) and heart transplantation (8%). The respiratory variation of peak early diastolic transmitral flow velocity by pulsed Doppler transesophageal echocardiography was 10.7% in patients with sinus rhythm and 18.1% in patients with atrial arrhythmia. Pericardial thickening was noted adjacent to the right-sided chambers in 19 patients, left-sided chambers in 10 patients, or both in 9 patients. All-cause 5-year mortality was 40% and unrelated to age, etiology, left ventricular systolic function and therapeutic course. There was a statistically
Introduction

Constrictive pericarditis and restrictive cardiomyopathy are clinical entities, which possess similar diagnostic signatures. However, constrictive pericarditis requires surgical treatment and is usually curable, while restrictive cardiomyopathy, short of cardiac transplantation, is treatable only by medical means and often responds unsatisfactorily. Therefore, the differentiation of constriction and restriction is important and has been challenging using various diagnostic techniques. Echocardiography is increasingly being used as an important noninvasive method for confirming the specific morphologic and hemodynamic abnormalities associated with either condition.

A subgroup of patients with mixed physiology of constriction and restriction has been previously reported; however, the clinical characteristics of these patients and their prognosis have not been well defined. Recently our group reported the long-term survival of patients with constrictive pericarditis after pericardiectomy over a 24-year period that was related to underlying etiology. However, classification of mixed constriction and restriction physiology was not considered in that previous study. Thus, the purpose of this study is to characterize the clinical and echocardiographic features of those patients with mixed constriction and restriction and to determine which variables might be associated with long-term mortality.

Methods

Study population

Out of a total of over 300 patients who were referred to the echocardiographic laboratory for determination of constrictive pericarditis or restrictive cardiomyopathy, 38 (12.7%) patients were identified as having features of mixed constrictive and restrictive physiology. This diagnosis was made according to 3 well-defined criteria: (1) localized thickening of the pericardium observed by transthoracic and/or transesophageal echocardiography (Fig. 1) and confirmed by magnetic resonance imaging (MRI) or computerized axial tomography (CT); (2) restrictive Doppler findings of transmitral and/or pulmonary venous flow velocity patterns (Fig. 1); and (3) no significant respiratory variations on early diastolic transmitral flow velocity (<25%). Restrictive filling was determined by ratio of peak early diastolic to atrial systolic transmirtal flow velocities (E/A) > 2, deceleration time of the E velocity profile (DT) < 150 ms, ratio of peak systolic to diastolic pulmonary venous flow velocities (S/D) < 0.5, peak atrial reversal pulmonary venous velocity (AR) > 0.35 m/s and difference of durations between atrial systolic transmitral and pulmonary venous atrial reversal flow velocities (AR-A) > 20 ms. In patients with prosthetic valve replacement, transmirtal flow velocity pattern was not used for the classification.

The pericardial thickening or calcification was confirmed by MRI (n = 32), CT scanning (n = 4), and cardiac catheterization (n = 2) including fluoroscopy. Data from cardiac catheterization (31 patients), endomyocardial biopsy (13 patients), pericardial biopsy (12 patients) and/or surgical findings (17 patients) were compatible with the echocardiographic diagnosis. On catheterization, there was dip and plateau physiology and equalization of pressures in 25 of the 31 patients. The overall mean pressures were as follows: RA = 18 ± 7 mmHg, RV systolic = 41 ± 12 mmHg, RV diastolic = 19 ± 8 mmHg, PA systolic = 40 ± 12 mmHg, PA diastolic pressure = 22 ± 7 mmHg, and PCWP = 22 ± 7 mmHg. An endomyocardial biopsy was performed on 13 patients and showed a variety of findings including 3 with lymphocytic infiltrate, 6 with fibrosis, 3 with no definite fibrosis, 1 with mild rejection, and 1 with moderate rejection. A pericardial biopsy was performed on 12 patients at the time of surgery and showed 10 with fibrosis, 5 with chronic inflammation, 4 with calcification, 2 with hemosiderin deposition, and 1 with malignant thymoma. The surgical findings of 17 patients at the time of pericardectomy showed 6 with thickened pericardium, 7 with calcification, 3 with adhesion, 1 with severe...
scarring, and 2 with a normal pericardium. Surgical findings were compatible with the echocardiographic diagnosis.

The study group included 30 men and 8 women, mean age was 57 ± 14 years (range: 29–82). We also performed survival analysis in 125 patients (mean age: 57 ± 13 years) who were diagnosed with pure constrictive pericarditis without restriction during the same observation period from our institution.8 The patients with constrictive physiology alone were assessed by transthoracic and transesophageal echocardiography with respiratory monitoring and MRI or CT. The diagnosis was confirmed by cardiac catheterization or surgical findings. The etiologies of the pure constriction group were idiopathic (54.4%), post cardiac surgery (29.6%), post radiation (9.6%), combination of cardiac surgery and radiation (0.8%), and miscellaneous (5.6%). Pericardial stripping was performed in 108 patients (86%). The study protocol was approved by the Institutional Review Board of The Cleveland Clinic Foundation.

Transthoracic echocardiography

A complete transthoracic echocardiogram was performed immediately before transesophageal echocardiography with commercially available echocardiographic equipment (Sonos 5500, Philips, Andover, MA, or Sequoia, Siemens, Mountain View, CA) using a 2.5 MHz transducer with simultaneous recordings of electrocardiographic and respiratory waveforms. M-mode echocardiography directed by 2-dimensional in parasternal short-axis or long-axis views was used to derive LV end-diastolic, end-systolic, and left atrial dimensions. LV posterior and septal wall thickness was also measured. LV ejection fraction was calculated according to the modified Simpson’s rule.9–11 Inter-observer variability for measuring LV ejection fraction was 6 ± 5% in our laboratory.

Transesophageal echocardiography

A complete transesophageal echocardiogram was performed using the same echocardiographic equipment for transthoracic echocardiography with respiratory monitoring. The transesophageal echocardiographic probe was passed according to the usual techniques, and the examination was performed in a standard manner.12

Transmitral flow velocities were recorded by pulsed Doppler echocardiography with the sample volume placed at the leaflet tips of the mitral valves. Pulsed Doppler examinations of the left upper pulmonary veins were performed by placing the sample volume 1–2 cm into the pulmonary veins proximal to where they enter the left atrium. From the velocity profiles obtained, early diastolic (E) and atrial systolic (A) transmitral flow velocities, deceleration time of E velocity (DT) and peak systolic (S), diastolic (D) and atrial reversal (AR) pulmonary venous flow velocities were measured. The E/A and S/D ratios were calculated. Time velocity integral of each wave was measured by offline analysis with digitizing the Doppler tracings.
Respiratory monitoring was performed with a nasal respirometer during echocardiographic examination. Doppler parameters were calculated as averaged values during inspiration or expiration for at least 3 respiratory cycles. In patients with atrial arrhythmia, 6 respiratory cycles were used. The respiratory variation of Doppler parameters \( \%E \) was calculated as \( \%E(\%) = \frac{[(\text{Expiration} - \text{Inspiration})/\text{Expiration}] \times 100} \). 

The myocardium and pericardium were assessed in the 4-chamber view, 2-chamber view, or transgastric short-axis view. A visual estimate of mitral and tricuspid valve regurgitation was graded as none, trivial, mild, moderate, or severe.

**Pericardial imaging**

MRI was performed with a 1.5 T scanner (Signa-Advantage 4 \( \times \) or 5 \( \times \); General Electronic Medical Systems, Milwaukee, WI), standard body coil, and an electrocardiographic gating system. In 3 patients, CT was performed instead of MRI. The transaxial orientation and equivalent 4-chamber and transgastric short-axis echo views were used. An apparent pericardial thickness of 3 mm or more is considered to be thickened pericardium.

**Clinical assessment**

Extensive chart review was performed with particular attention to etiology of the patients, especially previous history of cardiac surgery, prior radiation therapy, therapies including pericardial stripping, clinical course, and rhythm disturbance. The Social Security Death Index database\(^{17,18}\) was searched for the patient’s death date if they were not followed up by our hospital.

**Statistical analysis**

Results were expressed as mean value \( \pm \) SD. Survival analysis curves were created by the Kaplan–Meier method and potential prognostic variables were assessed by the log-rank test. A student t test was used for the comparison of parameters between the medication and surgical groups. \( p < 0.05 \) was considered statistically significant.

**Results**

**Etiology**

The major cause of mixed physiology was prior mediastinal radiation therapy \( (n = 19, 50\%) \). Eight patients had radiation therapy alone, while 11 patients underwent cardiac surgery after the radiation therapy. Nine of these 11 patients had coronary artery bypass graft (CABG), 1 patient had aortic and mitral valve replacements and 1 patient had both CABG and mitral valve replacement. The next major etiology was CABG without previous irradiation \( (n = 9, 24\%) \). Three patients \( (8\%) \) underwent orthotopic heart transplantation, 2 \( (5\%) \) had previous myocardial infarction, 1 \( (3\%) \) had mitral valve replacement and 4 patients \( (11\%) \) had idiopathic etiology.

**Clinical, M-mode, 2-dimensional and Doppler echocardiographic characteristics**

Major clinical characteristics of the 38 patients were summarized in Table 1. Mean heart rate was \( 87 \pm 23 \) (range: 58–147) BPM. Mean left atrial dimension was \( 4.4 \pm 0.8 \) (3.1–6.0) cm, mean LV end-diastolic dimension was \( 4.6 \pm 0.6 \) (3.4–5.8) cm, LV end-systolic dimension was \( 3.3 \pm 0.7 \) (2.1–4.8) cm, mean end-diastolic septal wall thickness was \( 1.1 \pm 0.3 \) (0.7–1.8) cm, mean end-diastolic posterior wall thickness was \( 1.1 \pm 0.3 \) (0.7–1.9) cm, and mean LV ejection fraction was \( 48 \pm 11 \) (25–65)\%. LV was dilated (end-diastolic diameter \( >5.0 \) cm) in 14 patients. Abnormal septal bounce was found in 21 patients. LV hypertrophy (mean wall thickness \( >1.3 \) cm) was found in 9 patients and 8 patients had regional LV wall motion abnormalities. The left atrium was dilated in 25 patients and the right atrium was dilated in 21 patients. Sixteen patients had significant mitral regurgitation (5 mild and 11 moderate) and 23 patients had significant tricuspid regurgitation (9 mild, 10 moderate and 4 severe). Transmitral and pulmonary venous flow velocity data and its respiratory variation are summarized in Table 2. We excluded 3 patients with prosthetic valves for the analysis of Doppler echocardiography. The respiratory variation of peak early diastolic transmitral flow velocity in patients without prosthetic valves was \( 10.7 \pm 5.9\% \) in sinus rhythm and \( 18.1 \pm 5.4\% \) in atrial arrhythmia. The respiratory variation of peak early diastolic pulmonary flow velocity in all subjects was \( 18.1 \pm 7.8\% \) in sinus rhythm and \( 19.9 \pm 6.0\% \) in atrial arrhythmia.

**Localization of thickened pericardium**

From the transthoracic and transesophageal echocardiographic assessments, thickened pericardium and/or myocardial tethering by the pericardium was located adjacent to the right-sided chambers in 19 patients, the left-sided chamber in 10 patients, or both sides in 9 patients. Localization...
of the increased pericardial thickness by echocardiography was confirmed by MRI or CT in all 38 patients.

Clinical outcome

The mean follow-up period was 4.0 ± 3.8 years (maximum, 13.4 years). Seventeen (45%) of the 38 patients had pericardial stripping and none of them underwent heart transplantation. There were 16 deaths (42%) that included 8 deaths observed in surgically treated patients and 8 deaths that occurred in medically treated patients. Between the surgically treated patients and medically treated patients, there were no significant differences in age, LV ejection fraction, localization of thickened pericardium, prior radiation and prior CABG. At 5 and 10 years, overall survival was 60 ± 8% and 50 ± 10%, respectively, in patients with mixed physiology. There was a significant difference between the survival rates over time in patients with mixed physiology and in patients with pure constriction.

Table 1  Patient characteristics

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<th>Case</th>
<th>Age/gender (years)</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Follow-up period (years)</th>
<th>Pericardial thickening</th>
<th>Rhythm</th>
<th>%E TMF-E (%)</th>
<th>%E PVF-D (%)</th>
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%E, respiratory variation; TMF-E, early diastolic transmitral flow velocity; PVF-D, diastolic pulmonary venous flow velocity; RAD, radiation therapy; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; MI, myocardial infarction; HT, heart transplantation; IDIO, idiopathic; Med, medical; Surg, surgical; RV, right ventricle; LV, left ventricle; SR, sinus rhythm; A fib, atrial fibrillation; A ft, atrial flutter.

A Died.
The diagnosis of mixed physiology predicted the survival and was independent of age. Age, LV ejection fraction, localization of thickened pericardium, previous radiation, previous CABG and treatment were not independent determinants of overall survival for mixed physiology patients (Fig. 3). These statistical results did not change when 3 patients with heart transplantation were excluded from the mixed physiology group. Perioperative mortality (30 days or in-hospital mortality) occurred in 1 patient (3%) due to bleeding complications.

**Discussion**

This study describes the clinical and echocardiographic characteristics as well as the outcome of patients with mixed constriction and restriction physiology. According to echocardiographic examination, the mixed physiology was a well-defined entity characterized by localized pericardial thickening accompanied with restrictive LV filling without significant respiratory variation. This mixed physiology occurred in 13% of patients who were being evaluated for complex diastolic dysfunction (restriction vs constriction-type patients). Prior radiation therapy and CABG were the predominant etiologic factors of these patients. All-cause mortality was substantial (40% at 5 years) and unrelated to age, etiology, LV systolic function or therapeutic course.
Definition of mixed physiology

Mixed constriction and restriction is defined as a combination of constrictive and restrictive physiologic mechanisms. In another words, this physiology is based on the evidence of both pericardial and myocardial abnormalities with markedly elevated LV end-diastolic or left atrial pressure. In this study, we diagnosed this disease mainly using two-dimensional and Doppler echocardiography and the diagnosis was confirmed by MRI (or CT), cardiac catheterization and/or endomyocardial biopsy. Echocardiography was a clinically useful noninvasive method to identify this entity.

Previous reports

Spodick reported that in some patients with constrictive pericarditis, the visceral pericardium was also involved and that involvement might have extended into the myocardium, resulting in mixed constriction and restriction. Hall et al. also described a case of a 69-year-old woman diagnosed as having constrictive pericarditis and restrictive cardiomyopathy secondary to radiation therapy for breast cancer. Oh et al. reported that 12% of patients with constrictive pericarditis demonstrate <25% of respiratory variation in early diastolic transmitral velocity. Their explanation for this finding was mixed constriction and restriction and/or marked increase of atrial pressure. In their report, out of 28 patients with suspected constrictive pericarditis who underwent exploratory thoracotomy or pericardiectomy, 3 patients had mixed physiology. The postoperative Doppler examination of those 3 patients remained abnormal (restrictive) and their symptomatic response was less satisfactory.

More recently, Klein et al. evaluated the utility TEE with respiratory monitoring for classification of patients with diastolic function in a large clinical practice. They classified 21 patients as having mixed constriction and restriction out of 192 patients who then underwent a transesophageal echocardiogram for evaluation of abnormal diastolic function. The major causes of the abnormality in this patient group were CABG (38%) and radiation therapy (33%).

Causes of mixed physiology

In this study, the 2 major causes of this abnormal physiology were therapeutic mediastinal radiation and cardiac surgery, especially CABG. This result

![Figure 3](https://academic.oup.com/ehjcimaging/article-abstract/8/3/185/2398038)
may be related to the increasing frequency of radiation and cardiac surgery as underlying causes of constrictive pericarditis in the United States.\textsuperscript{21–23} There are several outcomes in patients with mixed physiology after radiation therapy. Radiation induced cardiac disease produces a wide spectrum of abnormalities, including localized pericarditis, myocardial fibrosis, myocardial infarction and valvular dysfunction.\textsuperscript{24–26} In some patients, radiation itself may become a cause of both constrictive pericarditis and myocardial dysfunction. Endomyocardial biopsy may be especially important to assess the myocardial fibrosis, nonspecific inflammation and lymphocytic infiltration in these patients.\textsuperscript{6} In other patients, radiation-caused coronary stenosis or valvular dysfunction required CABG or valve replacement followed by postoperative constrictive pericarditis.

Incidence of constrictive pericarditis after CABG is reported to be 0.2--2.4%.\textsuperscript{27} An increased rate of graft occlusion has been suspected in CABG with postpericardiotomy syndrome.\textsuperscript{28} In the present series, 9 patients developed mixed dysfunction from CABG without prior radiation. Six patients had regional myocardial asynergy, however, 4 of them had asynergy prior to surgery. Myocardial infarction occurred postoperatively in 2 patients. The combination of the postoperative pericardial scarring and myocardial dysfunction would account for the mixed physiology.

**Respiratory variation of Doppler indices**

The Doppler findings of respiratory variation have been one of the major criteria to confirm constrictive physiology.\textsuperscript{2,4} Respiratory variation in mitral and tricuspid flow velocity is >25% in most cases with constrictive pericarditis, but <15% in most cases with restrictive cardiomyopathy. The sensitivity and the specificity were described to be as high as 85--90% in expert hands.\textsuperscript{29} In patients with mixed physiology, full respiratory variation in ventricular filling may be decreased because ventricular filling is limited mainly by a noncompliant myocardium rather than a constrictive pericardium. In addition, these patients usually have markedly increased left atrial and pulmonary venous pressure, which remain elevated after a small atrial contraction due to high end-diastolic LV pressure. In this situation, mitral valve opening occurs on the steeper than usual portion of the LV pressure curve. Thus, the normal inspiratory intrathoracic pressure decline may cause minimal change in pulmonary venous and left atrial pressure. Another possible cause for diminished respiratory variation is localization of thickened pericardium.\textsuperscript{30}

**Clinical implications**

The 10-year survival rate of our subjects was worse (50%) than that of patients with pure constriction (69%). The clinical course of patients with mixed disease was very complicated in each case. Since the pulmonary reserve of patients with mixed disease is more impaired when comparing with patients with pure constriction, cardiac death should be increased in patients with mixed physiology. Also, additional systemic disease, malignancy or pleuropulmonary disease may increase the risk of noncardiac deaths. There was no significant predictor for overall survival including pericardial stripping. In clinical settings, surgical treatment of these patients should be taken under adequate evaluation. Cardiac transplantation could be considered in selected patients without recurrent tumor and with good pulmonary reserve, particularly if severe ischemic or valvular heart disease coexists. From this point of view, it is very important to distinguish the patients with mixed disease from constrictive pericarditis without restriction. New echocardiographic techniques, such as tissue Doppler imaging and color M-mode, have been reported to be useful in distinguishing constrictive pericarditis from restrictive cardiomyopathy.\textsuperscript{31,32} These new echocardiographic techniques may be useful for further characterization of patients with this entity.

**Limitations**

First, this study was performed with a relatively small number of patients, however, it is the largest series to date describing this important clinical entity. Second, it is possible that our definition of mixed disease (localized pericardial disease, restrictive physiology and lack of respiratory variation) may not always be specific and there will always be exceptions; i.e., pure constriction without pericardial thickening or without significant respiratory variation.\textsuperscript{20,33} However, in our study, we did find transesophageal echocardiography to be very useful in showing the localized thickened pericardium or tethering; and we were able to assess the hemodynamics using both mitral inflow and pulmonary vein flow.\textsuperscript{6} Third, we did not have peak early diastolic mitral annular velocity and mitral flow propagation measurements in all of our subjects with mixed physiology; but we did find that these parameters seem to fall between those
measurements for constrictive pericarditis and restrictive cardiomyopathy in a subgroup of our mixed physiology patients. 

Conclusions

Due to the high mortality in patients with mixed constriction and restriction, discrimination of the entity from the patients with pure constriction is mandatory. Transthoracic and transesophageal echocardiography are helpful noninvasive techniques in the diagnosis and the understanding of the physiology of patients with this disease. Further large, possibly multicenter, registries will be necessary to better define this condition, follow the natural history and to determine the best treatment for these patients.

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