In this study we present a series of 5 cases that developed constrictive pericarditis after orthotopic heart transplantation. All 5 patients had pericardial effusion of non-infectious etiology in the early post-transplant period. They subsequently presented with heart failure unresponsive to standard medical management. The diagnosis was made by comprehensive echo-Doppler studies. Findings were confirmed at surgical inspection and complete pericardiectomy led to improvement in hemodynamics in 4 patients. One patient had relief from constriction but died of non-cardiac complications. One patient with constriction has been re-listed for transplantation due to intermittent heart block and associated cardiac allograft vasculopathy. Early diagnosis of pericardial constriction after orthotopic heart transplantation requires a high index of clinical suspicion and optimal use of Doppler echocardiography. Early diagnosis and timely surgical pericardiectomy may correct this condition entirely and result in satisfactory long-term results.

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KEYWORDS: pericardial constriction; cardiac transplant; echocardiography

Orthotopic heart transplantation (OHT) has become an accepted form of therapy for end-stage heart disease with 5- and 10-year survival rates of 75% and 55%, respectively.¹ Acute rejection, infection, and cardiac allograft vasculopathy have been recognized as the major causes of morbidity and mortality in these patients. Constrictive pericarditis may follow any cardiac surgical procedure, including coronary bypass, valvular replacement surgery and corrective surgery for congenital heart disease.²–⁸ Cardiac surgery is reported to be the leading cause of pericardial constriction in patients with an identifiable etiology.²–⁶ The incidence of pericardial constriction after cardiac surgery varies from 0.1% to 0.3%.⁵ There have also been rare case reports of constrictive pericarditis after cardiac transplantation surgery; several of these have described constriction in association with purulent pericarditis and mediastinitis.⁹–¹⁶ In this report, we describe the largest clinical experience of post-transplant pericardial constriction of non-infectious etiology. We review the literature and report the incidence, etiology, diagnostic features, and management of this condition.

Methods

We performed a search of our institution’s echocardiographic database and identified all patients who had evidence of pericardial constriction after orthotopic heart transplantation. Our surgical database was also searched to capture cases that had undergone peri-cardiectomy for post-transplant constriction. We then proceeded to review their medical and surgical records and collected information regarding clinical, imaging, hemodynamic, and pathologic results. The number of diagnosed and treated rejection episodes were obtained. All patients received intravenous steroids peri-operatively and were continued on a tapering dose of oral prednisone as part of a triple-drug immunosuppressive regimen. The follow-up period ranged from 7 months to 11 years.
Surgical technique

Surgical management of the pericardium at the time of OHT consisted of excision of a generous segment of the anterior pericardium after excision of the native heart and prior to implantation of the donor organ. This window ends approximately 2 cm anterior to the left phrenic nerve. This communication between the pericardial and the left pleural spaces reduces the incidence of large pericardial fluid collection. Such partial pericardiectomy is routinely performed in patients with first-time sternotomy; however, in patients with multiple previous sternotomies and/or cardiac operations, the presence of fibrous adhesions within the middle mediastinum and the pleural spaces may not allow much pericardial resection. In such cases when the mediastinal tissue is fixed or indurated with extensive adhesions, we opt not to take down the adhesions. Routinely, however, large chest tubes are used to drain the pericardial and left pleural spaces. Primary closure of the sternotomy is performed after the transplantation procedure and no attempt is made to close the pericardium over the grafted organ.

When pericardial constriction occurs after heart transplantation, re-operation is performed via re-do sternotomy. Cardiopulmonary bypass may be necessary for complete and adequate pericardiectomy. Surgical bleeding during pericardiectomy is usually controlled after reversal of heparinization.

Results

Between January 1986 and May 2009, 127 adult OHT procedures were performed at our institution. After OHT, serial echocardiographic studies are performed per institutional protocol. Review of this database revealed the presence of pericardial effusions of varying sizes in 53 patients (42% of all cases) in the early post-operative period (average 27 days). In the great majority of cases, the effusion resolved spontaneously in the subsequent 3 months without consequences. Five patients developed diagnostic features of pericardial constriction (4% of all transplant recipients; 9% of patients developing effusions) and constitute the basis of this report. In 4 cases, surgical findings and pathologic specimens at pericardiectomy confirmed the clinical diagnosis.

A summary of our patients’ demographics, clinical and surgical characteristics, and ancillary data is presented in Table 1.

Time to development of constriction varied from 3 weeks to 11 years after OHT. All patients presented with progressive symptoms of right-sided heart failure. Echocardiography was the initial imaging study to suspect pericardial constriction in all patients. Hemodynamic studies were performed in 4 and computed tomography in 2 patients. Endomyocardial biopsy at variable intervals was performed on all individuals; low-grade rejection requiring adjustment of immunosuppressant drugs was found in 4 of 5 cases.

Four patients underwent successful pericardiectomy with satisfactory intra-operative results. However, despite clear evidence of restoration of near-normal hemodynamics and cardiac function, 1 patient died 30 days after pericardiectomy as a consequence of widespread, extensive, multifocal herpetic ulcerations involving the entire gastrointestinal tract.

Summaries of our 5 cases are presented in what follows.

Case 1

A 49-year-old man with severe ischemic cardiomyopathy underwent OHT. A follow-up echocardiogram 3 months later revealed a large pericardial effusion with features of tamponade that led to prompt pericardiocentesis; the effusion re-accumulated and led to a second pericardiocentesis 6 weeks later. He remained clinically stable until 14 months after the transplant when he presented with right-sided heart failure with lower extremity edema and ascites. Echocardiographic examination revealed a thick pericardium overlying the right atrium and right ventricle with markedly elevated right atrial (RA) pressure, features consistent with pericardial constriction.

During pericardiectomy, the thick, fibrotic pericardium was confirmed and epicardial decortication completed the procedure. The patient was discharged home 2 days later. At his most recent visit 5.7 years after pericardiectomy, he was asymptomatic and echocardiography showed normal graft function and filling pressures.

Case 2

A 56-year-old man with dilated cardiomyopathy underwent OHT. An echocardiogram 2 months later showed a small- to

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at the time of diagnosis (years)</th>
<th>Gender</th>
<th>Post-transplant pericardial effusion</th>
<th>Pericardiocentesis prior to pericardiectomy</th>
<th>Rejection episodes</th>
<th>Time to constriction development</th>
<th>Outcome</th>
<th>Long-term follow-up after pericardiectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (A.J.)</td>
<td>49</td>
<td>M</td>
<td>Yes</td>
<td>2</td>
<td>2</td>
<td>14 months</td>
<td>NYHA I</td>
<td>5.7 years</td>
</tr>
<tr>
<td>2 (M.M.)</td>
<td>57</td>
<td>M</td>
<td>Yes</td>
<td>0</td>
<td>5</td>
<td>13 months</td>
<td>NYHA I</td>
<td>8.9 years</td>
</tr>
<tr>
<td>3 (N.R.)</td>
<td>47</td>
<td>F</td>
<td>Yes</td>
<td>0</td>
<td>0</td>
<td>3 weeks</td>
<td>NYHA II</td>
<td>9.4 years</td>
</tr>
<tr>
<td>4 (A.L.)</td>
<td>35</td>
<td>M</td>
<td>Yes</td>
<td>0</td>
<td>9</td>
<td>5 years</td>
<td>Expired</td>
<td>N/A</td>
</tr>
<tr>
<td>5 (P.D.)</td>
<td>28</td>
<td>M</td>
<td>Yes</td>
<td>0</td>
<td>2 (humoral)</td>
<td>11 years</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1 Patients’ Salient Clinical Characteristics and Outcomes
moderate-sized localized pericardial effusion that resolved spontaneously. Severe constriction was diagnosed by echocardiography 13 months after OHT. Diagnosis was supported by hemodynamic studies.

During radical pericardiectomy, a thickened pericardium and a dense epicardial peel over the right atrium and ventricle were found. The patient had a favorable postoperative course and was discharged 5 days after pericardiectomy.

He was most recently seen 8.9 years after pericardiectomy and has continued to have no cardiac symptoms; his echocardiogram showed normal ventricular function and filling pressures.

Case 3

A much earlier presentation of constriction was seen in our third case, a 47-year-old woman who had undergone transplant for sarcoid-related cardiomyopathy. Only 3 weeks after OHT, she presented with hypotension, leg edema, and ascites. Echocardiogram revealed bloody effusion, clotted blood circumferentially in the pericardium with thickened and fused pericardial layers, and high RA pressure. She underwent urgent phrenic-to-phrenic pericardiectomy. Immediately after resection, an improvement in blood pressure and a drop in central venous pressure (CVP) were noted. A pericardial pathologic specimen showed sarcoid granulomatous lesions and pericardial thickness of up to 1.5 cm. She was discharged in stable condition 2 days after pericardiectomy.

On a recent visit at 9.4 years after OHT, she reported moderate exertional dyspnea related to diastolic dysfunction, severe tricuspid regurgitation, and pulmonary hypertension.

Case 4

A 29-year-old man with palliated complex congenital heart disease underwent OHT. Several Grade 2R rejection episodes were managed with intensification of immunosuppressants. A self-resolving, small pericardial effusion was noted as early as 19 days after OHT. Five years after transplant, heart failure symptoms developed and chest X-ray showed a new pleural effusion. Echo-Doppler studies showed normal systolic function and evidence of pericardial thickening and enhanced ventricular interdependence by 2-dimensional echocardiography and respirophasic valvar flow changes (Figures 1 and 2). Echo-cardiography also showed left pleural effusion. Right heart catheterization demonstrated classical hemodynamics of constriction (Figure 3). A cardiac computerized tomography (CT) scan showed regional pericardial thickening of up to 6 mm (Figure 4).

Myocardial biopsy showed no evidence of rejection. At the time of pericardiectomy, the patient was critically ill as a consequence of marked coagulopathy secondary to liver dysfunction (INR 7.0), decreased renal function (creatinine 2.9 mg/dl), nutritional depletion, oliguria, hypotension, and hypoxemia. Marked pericardial thickening (up to 8 mm) with dense epicardial peel causing extreme cardiac constriction was noted during pericardiectomy (Figure 5). Pericardiectomy and epicardial decortication were performed using cardiopulmonary bypass, after which a drop in CVP from 42 to 15 cm H2O and a brisk increase in urine output were noted. He was extubated 72 hours after pericardiectomy with marked improvement in hemodynamics and heart failure symptoms. Intermittent hemodialysis was required. Three weeks after, he developed a surgical abdomen with refractory shock; despite resuscitative efforts, he died 31 days after pericardiectomy. Post-mortem examination revealed widespread multifocal herpetic ulcerations involving the entire gastrointestinal tract.

Case 5

A 29-year-old man with viral cardiomyopathy underwent OHT and developed a spontaneously resolving pericardial effusion 2 weeks after transplantation. Incipient echocardio-
graphic evidence of pericardial constriction was first noted 11 years after OHT, as evidenced by preserved left ventricular systolic function, normal valve function, a non-collapsible inferior vena cava, pleural effusion (Figure 6), and increased transvalvar respirophasic flow variation. The pericardium was only minimally thickened by echocardiography and showed normal systolic function and preserved systolic and E' velocities by Doppler tissue imaging (Figure 6). These findings favored constriction rather than restriction or rejection. Chest CT showed normal thickness pericardium (Figure 7); however, the CT showed other features of volume overload, including dilation of inferior vena cava and pleural effusion (Figure 7).

He was recently admitted with an episode of syncope due to complete heart block, presumably due to humoral rejection and allograft vasculopathy. In addition to plasmapheresis and intensification of immunosuppressants, he has been wait-listed for re-do heart transplant.

Discussion

Post-transplant constrictive pericarditis

Constrictive pericarditis is an infrequent, but well-documented complication of cardiac surgery.2–8 It was first reported in 19722 and may develop after any cardiac surgical procedure, including coronary bypass grafting, valve surgery, and repair of congenital lesions.2–8 The incidence of
post-surgical constriction ranges from 0.1% to 0.3%.\textsuperscript{5–7} In developing countries, the most common etiology of constriction continues to be tuberculosis.\textsuperscript{8} In the United States, however, cardiac surgery has become the leading cause of constriction and accounts for 18%\textsuperscript{7} to 37%\textsuperscript{5} of cases with an identifiable etiology.

Constriction has also rarely been reported after cardiac transplantation.\textsuperscript{9–16} Review of the transplant literature reveals a total of 17 cases of pericardial constriction reported in 8 publications (Table 2). In previous reports, the time to recognition of constriction ranged from 1 month to 2 years\textsuperscript{9–16}; we observed its development as early as 3 weeks and as late as 11 years after OHT. This condition affected approximately 1.5% of cases in previous clinical\textsuperscript{10,13} and 2.6% in post-mortem\textsuperscript{11} reports. In our series, it developed in 5 of 127 (4%) of adult cardiac transplants. The true incidence of post–cardiac transplant constriction remains elusive; patients with pericardial constriction causing mild heart failure may respond to diuretics and are unlikely to undergo testing to establish the diagnosis. Similarly, refractory heart failure in transplant recipients may be treated as rejection and restrictive cardiomyopathy rather than constriction. This uncertainty may have delayed the diagnosis in Patients 4 and 5 in the present series, and has been recognized previously.\textsuperscript{15}

**Pathogenesis**

It has been suggested that pericardial constriction after cardiac surgery is related to peri-operative pericardial injury or inflammation and exposure of the injured serosal surface to intra-pericardial bleeding.\textsuperscript{3} In addition, pericardial irrigation with povidone–iodine in the presence of serosal injury may precipitate a pericardial fibrotic reaction.\textsuperscript{2,3} Clinical features suggestive of the post–pericardiotomy syndrome were noted in 62% of cases in one large series of post-surgical pericardial constriction.\textsuperscript{3} Pericardial injury, irritation, bleeding, and mediastinal infections initiate a fibrotic reaction that predisposes to the subsequent development of constriction in heart transplant recipients. A review of the 17 reported cases of post-transplant constriction showed that 4 cases had mediastinal or wound infection, and 2 had infected and 10 non-infected pericardial effusion after OHT. In our series, all 5 cases developed a non-infected pericardial effusion or hematoma after surgery. Pericardiocentesis was performed in 1 patient.

**Diagnosis**

The diagnosis of constrictive pericarditis should be strongly considered in cardiac transplant recipients who present with

![Figure 5](image5.png) Pericardial specimen shows markedly thickened pericardium.

![Figure 6](image6.png) Select echo-Doppler images from Patient 5 showing dilated inferior vena cava (IVC) in the left panel. The liver is congested and right pleural effusion (PE) is noted in the middle panel. Tissue Doppler imaging from lateral mitral annulus shows high systolic (S) and $E'$ tissue velocities. The pericardium was minimally thickened and fused on 2-dimensional imaging.

![Figure 7](image7.png) Computed tomography image of the chest shows normal pericardial thickness (arrow) and right pleural effusion (PE).
symptoms of predominant right heart failure and a history of early post-operative pericardial effusion, bleeding, hematoma, or mediastinal infection. In patients with heart transplant, however, rejection and restriction must be excluded.\textsuperscript{17–19} Echocardiography is usually the first study performed and provides guidance regarding selection of appropriate complimentary procedures such as CT, magnetic resonance, and cardiac catheterization. The detection of thickened pericardium of \textgreek{h}3\,mm may be of help in diagnosing pericardial constriction.\textsuperscript{20,21} Pericardial thickness can be measured by transthoracic and transesophageal echocardiography (Figure 1), and also by CT (Figures 4 and 7). Of note, an isolated thickened pericardium in the absence of abnormal hemodynamics does not imply constriction. On the contrary, in 21\% of patients with post-surgical constriction, a normal pericardial thickness was encountered on cardiac CT.\textsuperscript{3} Talreja et al described a normal pericardial thickness in 18\% of patients undergoing pericardiectomy for constriction.\textsuperscript{21} Clinical, echo-Doppler and hemodynamic features of constriction but normal pericardial thickness on cardiac CT (Figure 7) were found in 1 patient in our series.

Patients with constrictive pericarditis demonstrate the characteristic features of dissociation of intracardiac and intrathoracic pressures and enhanced ventricular interdependence. These abnormalities lead to inspiratory leftward septal shift on 2-dimensional echocardiography (Figure 1) and dynamic respirophasic flow variation in intracardiac flow velocities. Doppler echocardiography demonstrates an increase in mitral and aortic flow velocities in excess of 25\% during expiration compared with inspiration (Figure 2). Elevated right atrial pressure produces inferior vena cava dilation and lack of inspiratory collapse. High cardiac filling pressures cause pleural effusion and ascites (Figures 4, 6, and 7). Cardiac catheterization shows high right atrial mean pressure with a rapid “y” descent and lack of respiratory variation (Figures 3 and 8). Right ventricular pressure tracing shows a characteristic dip-and-plateau, or square-root pattern (Figure 3). Enhanced ventricular interdependence leads to a rise in right ventricular systolic pressure due to increased right ventricular filling during inspiration and a reciprocal decrease in left ventricular\textsuperscript{22–24} and aortic pressures (Figures 3 and 8).

**Management and outcomes**

Pericardiectomy and epicardial decortication relieve the restraint on cardiac filling and result in marked symptomatic

<table>
<thead>
<tr>
<th>Investigators (date)</th>
<th>( n )</th>
<th>Incidence</th>
<th>Wound\textsuperscript{a}</th>
<th>Post-transplant pericardial effusion</th>
<th>Time to constriction development</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from Copeland (1986)</td>
<td>1</td>
<td>NA</td>
<td>Serratia effusion pericardial (1 of 1)</td>
<td>NA</td>
<td>15 months</td>
<td>NYHA I</td>
</tr>
<tr>
<td>Data from Carrier (1994)</td>
<td>2</td>
<td>1.5% (2 of 133)</td>
<td>NA</td>
<td>Pericardial hematoma (2 of 2)</td>
<td>1 and 12 months</td>
<td>NYHA I (1) persistent symptoms and SCD (1)</td>
</tr>
<tr>
<td>Data from Loire (1994)</td>
<td>5</td>
<td>2.6% (5 of 191)</td>
<td>NA</td>
<td>Pericardial effusion (5 of 5)</td>
<td>( \leq 10 ) weeks (4), ( \approx 10 ) weeks (1)</td>
<td>Expired (4), retransplant (1)</td>
</tr>
<tr>
<td>Data from Hinkamp (1994)</td>
<td>4</td>
<td>1.4% (4 of 295)</td>
<td>Staphylococcal pericardial effusion (1 of 4)</td>
<td>Pericardial effusion (2 of 4)</td>
<td>2, 4, 7, 24 months</td>
<td>NYHA I (1), NYHA IV, home inotropes (1), expired (1), retransplant (1)</td>
</tr>
<tr>
<td>Data from Roca (1995)</td>
<td>2</td>
<td>NA</td>
<td>Staphylococcal mediastinitis (1 of 2)</td>
<td>NA</td>
<td>4 and 5 months</td>
<td>NYHA I (1), NYHA II (1)</td>
</tr>
<tr>
<td>Data from Rose (2002)</td>
<td>1</td>
<td>NA</td>
<td>Empyema (1 of 2)</td>
<td>NA</td>
<td>2 years</td>
<td>Expired due to graft arteriopathy</td>
</tr>
<tr>
<td>Data from Ramana (2005)</td>
<td>1</td>
<td>NA</td>
<td>Pseudomonas mediastinitis (1 of 1)</td>
<td>No</td>
<td>3 months</td>
<td>Stable, discharged (NYHA NA)</td>
</tr>
<tr>
<td>Data from Kumar (2008)</td>
<td>1</td>
<td>NA</td>
<td>Wound infection (1 of 1)</td>
<td>Pericardial effusion (1 of 1)</td>
<td>5 months</td>
<td>NYHA I</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association (heart failure classification); NA, not applicable; SCD, sudden cardiac death.

\textsuperscript{a}Infection/mediastinitis/pericarditis/empyema.
improvement in the majority of patients. Peri-operative mortality appears to be related to etiology; it was reported to be 2.7% in idiopathic, 8.3% in post-surgical, and 21.4% in post-radiation pericardial constriction.5 Long-term survival is adversely impacted by post-radiation etiology, advanced constrictive, calcification, older age, left ventricular systolic dysfunction, higher pulmonary pressure, and renal dysfunction.5,7

In post-transplant pericardial constriction, good outcomes after pericardiectomy are related to an early diagnosis. It is evident that the coexistence of post-transplant restrictive cardiomyopathy is associated with poor long-term results even after pericardiectomy is performed.13

Previous reports in which postoperative clinical data are available have demonstrated that approximately 50% of patients enjoy satisfactory, long-term, symptom-free survival.9,10,12–16 Our results confirm the potential for excellent long-term outcomes when the condition is diagnosed and treated early. When the diagnosis is delayed or recognized late, this condition is associated with malnutrition, coagulopathy, and liver and kidney insufficiency. These patients can be critically ill and their post-pericardiectomy outcome may be poor. Conservative management with clinical and echocardiographic surveillance appears to be a safe strategy in minimally symptomatic individuals.

In conclusion, constrictive pericarditis should be strongly considered in heart transplant patients presenting with heart failure with preserved systolic function. The index of suspicion should be higher in transplant recipients with a history of post-operative pericardial effusion, hematoma, or mediastinal infection. A complete echo-Doppler examination will provide definitive information in the majority of patients. CT and cardiac catheterization provide complementary information. Pericardiectomy with epicardial de-cortication should be considered early in symptomatic cases and is generally associated with favorable long-term results.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References