Pericardial Adaptation in Severe Chronic Pulmonary Hypertension

An Intraoperative Transesophageal Echocardiographic Study

Daniel G. Blanchard, MD, and Howard C. Dittrich, MD

Background. The pericardium both limits cardiac distension and accentuates ventricular interdependence. Although this effect appears modest under normal circumstances, the pericardium markedly restricts acute cardiac enlargement. Animal studies have demonstrated gradual pericardial adaptation and expansion in chronic volume overload and cardiomegaly, but the pericardial response in humans with cardiac hypertrophy and enlargement has not been examined fully. To investigate this further, 14 patients with right ventricular hypertrophy and cardiomegaly secondary to chronic pulmonary thromboembolic disease and severe pulmonary hypertension were studied during pulmonary thromboendarterectomy.

Methods and Results. Simultaneous intraoperative transesophageal Doppler echocardiography and direct biventricular hemodynamic measurements were performed at steady state immediately before and after pericardiectomy. All hemodynamic variables showed no significant change before and after pericardiectomy, including heart rate (76±16 versus 75±15 beats per minute), mean pulmonary arterial pressure (46.3±11.1 versus 45.5±11.7 mm Hg), cardiac index (1.8±0.5 versus 2.0±0.6 l/min/m²), left ventricular end-diastolic pressure (5.9±5.7 versus 7.1±5.0 mm Hg), and right ventricular end-diastolic pressure (7.9±6.6 versus 8.0±6.7 mm Hg). Similarly, there were no significant changes in all Doppler echocardiographic parameters, including right ventricular end-diastolic area (23.2±5.7 versus 22.6±5.4 cm²), left ventricular end-diastolic area (15.3±5.9 versus 15.5±4.4 cm²), the position of the interventricular septum, and the Doppler-derived mitral inflow measures of diastolic function.

Conclusions. The pericardium appears to have little influence on the marked cardiac and septal deformations seen in patients with chronic, severe right ventricular pressure overload and cardiomegaly. This study confirms that the human pericardium is capable of adapting over time to changes in cardiac size and geometry. (Circulation 1992;85:1414–1422)

KEY WORDS • ventricular function • echocardiography, transesophageal • hypertension, pulmonary • pericardium

The normal pericardium both limits cardiac distension and accentuates ventricular interdependence.1 Work in animal and human models has demonstrated that these effects are modest in the normally functioning heart.1,2 Because of its low compliance at higher volumes, however, the pericardium markedly limits acute cardiac enlargement.3 This effect, though, is not constant over time, and LeWinter and Pavelec4 and Freeman and LeWinter4 have shown that the pericardium is a dynamic structure: In a canine model of chronic volume overload and cardiac enlargement, the influence of pericardial restraint gradually diminished, with a concomitant increase in pericardial mass and a rightward shift of the pericardial pressure-volume curve. This same attenuation of restraint has long been recognized in chronic pericardial effusions.6

Ventricular interdependence and the pericardial influence on cardiac geometry have been difficult to examine in humans, and extrapolations from animal data may not be valid. For example, several animal studies have demonstrated significant pericardial coupling of right and left ventricular pressures and geometry,7,8 whereas two studies of patients undergoing coronary bypass surgery have reported little or no effect of the pericardium on ventricular pressures and volumes or on septal position and contour.2,9 In one of these series,2 no patients had ventricular hypertrophy or dilation, and in the other,9 all patients had normal left ventricular function and no previous myocardial infarctions. In patients with chronic ventricular hypertrophy and enlargement, little is known about pericardial restraint and its effects on cardiac shape and hemodynamics.

Chronic pulmonary hypertension can lead to severe right ventricular hypertrophy and overall cardiac enlargement. A specific form of pulmonary hypertension, chronic pulmonary thromboembolic disease, is a surgically reversible disorder,10 and striking improvements in
biventricular hemodynamics and dimensions have been observed in a number of reports. This condition and its therapy provide a unique opportunity to assess the influence of the pericardium in a model of chronic right ventricular pressure overload and hypertrophy. The purpose of this study was to analyze acute changes in diastolic cardiac geometry and hemodynamics in patients with severe, chronic pulmonary hypertension when the restraining forces of the pericardium were removed at the time of surgery.

Methods

Study Population

This study was approved by the Institutional Review Board on Human Research of the University of California San Diego. Informed consent was obtained from all patients. Fourteen patients who underwent pulmonary thromboendarterectomy were studied, all in New York Heart Association functional class III or IV at the time of surgery. The group consisted of seven men and seven women (mean age, 53.9±10.9 years; range, 39–69 years) with an average duration of cardiopulmonary symptoms before surgery of 59±47 months (range, 6–156 months). All had echocardiographically proven right ventricular enlargement and hypertrophy before surgery. Patients were enrolled on the basis of their willingness to participate in the study, without the investigators' prior knowledge of the subject's hemodynamic or echocardiographic evaluation.

The evaluation of these patients before surgery has been described previously, and all had documented proximal, surgically resectable pulmonary thrombi.

Study Protocol

All patients underwent standard cardiac anesthesia with high-dose narcotic and were mechanically ventilated. Hemodynamic variables were monitored intraoperatively with radial artery and thermodilution pulmonary artery catheters. After induction of anesthesia, a transesophageal echocardiographic probe (5 MHz, Hewlett-Packard Co., Andover, Mass.) was passed to the distal esophagus, and optimal visualization of the heart was confirmed. The chest was then opened and the heart exposed. With the pericardium still closed, two 18-gauge needles were inserted into the heart, one into the right ventricular cavity and one into the left. Each needle was attached by 6-in. fluid-filled tubing to a pressure transducer (Abbott Critical Care, Chicago, Ill.) and a multichannel recorder. Each transducer was zeroed at the level of the right ventricular free wall. Before sets of measurements were made, each patient had been hemodynamically stable for several minutes. Simultaneous pressure recordings from the right ventricle, left ventricle, pulmonary artery, and radial artery were obtained during the entire respiratory cycle. Coincident with this, transesophageal echocardiographic images were recorded on 0.5-in. videotape, both in the four-chamber and left ventricular short-axis (papillary...
FIGURE 2. Echocardiographic left ventricular short-axis (top panel) and four-chamber (bottom panel) end-diastolic views, with computerized calculation of left ventricular short-axis end-diastolic area (top panel) and four-chamber right and left ventricular end-diastolic areas (bottom panel).
muscle level) views. Pulsed-wave Doppler tracings through the mitral valve were also recorded. The videotape and pressure recordings were synchronized by use of simultaneous electronic calibration marks in the accompanying electrocardiographic tracings. Cardiac output and index, systemic vascular resistance, and pulmonary vascular resistance were calculated by thermodilution technique. After data collection was complete, the pericardium was opened wide from apex to base, and sutures were placed to isolate the heart from the pericardium and form a pericardial cradle. All measurements were then repeated. No significant changes were made in fluid or anesthetic management during this time period. The intraventricular needles were then removed, and pulmonary thromboendarterectomy was done.

**Analysis of Data**

*Two-dimensional echocardiography.* To document the extent of cardiac enlargement in the study patients before surgery (all had cardiomegaly on the preoperative chest radiograph), total cardiac area at end diastole was measured in the transthoracic apical four-chamber view. These values were corrected for body surface area and compared with 14 consecutive controls with normal echocardiographic studies. Transthoracic and transesophageal echocardiographic images were displayed and analyzed on a commercially available off-line system (MicroSonics, Indianapolis, Ind.). The end-systolic image was defined as the frame in which the smallest left ventricular size was present, and the end-diastolic image was selected as the frame at the peak of the R wave on the ECG.

The eccentricity index, a measure of interventricular septal flattening and distortion initially described for transthoracic echocardiography, was adapted to transesophageal views and determined at end diastole and end systole as the ratio of two perpendicular diameters of the left ventricle in the short axis at the level of the papillary muscles (Figure 1). Left ventricular end-diastolic and end-systolic areas were determined in both short-axis and four-chamber views; right ventricular end-diastolic and end-systolic areas were determined

**TABLE 1. Hemodynamic Variables**

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Before pericardiomy</th>
<th>After pericardiomy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>76±16</td>
<td>75±15</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>76.9±13.1</td>
<td>78.2±12.0</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>46.3±11.1</td>
<td>45.5±11.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l/min ∙ m²)</td>
<td>1.8±0.5</td>
<td>2.0±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>5.9±5.7</td>
<td>7.1±5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular end-diastolic pressure (mm Hg)</td>
<td>7.9±6.6</td>
<td>8.0±6.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.
All values are mean±SD, averaged for 14 patients.
only in the four-chamber view (Figures 2A and 2B). By use of simultaneous ECG calibration marks on both videotape and strip-chart recordings, corresponding left and right ventricular pressures were determined for each area calculation. As another index of interventricular septal deformation, distances from the right ventricular free wall to the interventricular septum, from the septum to the left ventricular free wall, and from the right ventricular free wall to the left ventricular free wall were measured in the four-chamber end-diastolic images (Figure 3); these determinations were made perpendicular to the interventricular septum 2 cm distal to the level of the mitral valve annulus.

To investigate whether a particular phase of diastole was more affected by pericardiotomy, serial left ventricular areas were measured during early, mid, and late diastole at end expiration in several patient studies (in the short-axis view, papillary muscle level). These values were plotted with corresponding left ventricular pressures to create diastolic pressure–area curves.

**Pulsed-wave Doppler echocardiography.** Pulsed-wave Doppler echocardiography was performed in the four-chamber transesophageal view, with sample volumes positioned on the ventricular aspect of the mitral annulus, where maximal peak flow velocities were obtained with minimal spectral broadening. No correction was made for the angle between the interrogating Doppler beam and the mitral inflow, but this angle was estimated to be less than 20° in all cases. Mitral inflow was recorded at 100-mm/sec paper speed. Peak early and late diastolic velocities of three consecutive cardiac cycles were measured, and the mean ratio of these velocities was calculated. Heart rates before and after pericardiotomy were recorded.

**Statistical Analysis**

All values are expressed as mean±SD. Comparisons among groups were performed by Fisher's exact and unpaired t tests. Differences were considered significant at p<0.05. To assess observer variability, random echocardiographic images and hemodynamic tracings were reanalyzed by the two authors in a blinded manner.

**Results**

**Hemodynamic Findings**

Hemodynamic data before and after pericardiotomy are shown in Table 1 and Figures 4 and 5 (all measurements were made at end expiration). No significant differences were observed in any hemodynamic parameter, including mean arterial pressure, mean pulmonary artery pressure, left and right ventricular end-diastolic pressures, cardiac index, and heart rate. The lack of change in these averaged values was not a result of a wide scatter of data.

**Figure 4.** Panel A: Graph of mean arterial pressure before (PRE) and after (POST) pericardiotomy. Panel B: Graph of mean pulmonary arterial pressure before (PRE) and after (POST) pericardiotomy.

**Figure 5.** Panel A: Graph of left ventricular (LV) end-diastolic pressure before (PRE) and after (POST) pericardiotomy. Panel B: Graph of right ventricular (RV) end-diastolic pressure before (PRE) and after (POST) pericardiotomy.
points, as the variables from each patient usually showed little change before and after pericardiotomy.

Right and left ventricular end-diastolic pressures, mean arterial pressure, and mean pulmonary artery pressure were also measured at peak positive-pressure inspiration. Although these measurements were generally 3–5 mm Hg greater than end-expiratory pressures, the trend was not statistically significant (Table 2). There was also no significant difference in any peak-inspiratory parameter before and after pericardiotomy (Table 2).

**Echocardiographic Findings**

Transthoracic echocardiographic measurement of total cardiac area from the apical four-chamber view (corrected for body surface area) was significantly greater in the 14 patients than in the 14 controls (68.4±10.2 versus 51.6±4.3 cm²/m², p<0.001).

Echocardiographic and Doppler data before and after pericardiotomy are shown in Table 3. As in the hemodynamic findings, there were no significant changes in any parameter after the pericardium was opened, including left ventricular end-diastolic area (in both short-axis and four-chamber views), right ventricular end-diastolic area (in four-chamber view), interventricular septum–to–right ventricular free wall end-diastolic diameter, interventricular septum–to–left ventricular free wall end-diastolic diameter, and the eccentricity index (both end-systolic and end-diastolic). In addition, there were no changes in the absolute Doppler-derived velocities of early (E) and late (A) diastolic filling or the Doppler E/A mitral inflow ratio.

The left ventricular pressure–area relations from two patients before and after pericardiotomy are shown in Figures 6A and 6B. Determinations of left ventricular area in the short-axis/mid–papillary-muscle view during diastole were plotted against simultaneous left ventricular pressure measurements. In these two examples, left ventricular filling characteristics throughout diastole were nearly superimposable.

Intraobserver and interobserver variability was <5% in hemodynamic pressure tracing analysis and <10% in echocardiographic area and dimension calculations.

**Discussion**

The influence of the pericardium on cardiac shape and dimension has been difficult to study in humans, especially in states of chronic cardiac enlargement. Although research in canine models has demonstrated that gradual increases in pericardial mass and compliance accompany chronic cardiomegaly, it is unknown to what extent these findings are applicable in humans. The patients in this study, all of whom had right ventricular hypertrophy and severely dilated right-sided cardiac chambers from longstanding, severe pulmonary thromboembolic disease, provided an opportunity to investigate the restraining influence of the pericardium in a chronic pressure-load state.

### Table 2. Inspiratory and Expiratory Hemodynamics Before and After Pericardiotomy

<table>
<thead>
<tr>
<th>Parameter (mm Hg)</th>
<th>Inspiration (mm Hg)</th>
<th>Expiration (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>LVEDP</td>
<td>8.1±4.5</td>
<td>8.0±4.2</td>
</tr>
<tr>
<td>MAP</td>
<td>83.8±11.0</td>
<td>83.6±11.1</td>
</tr>
<tr>
<td>RVEDP</td>
<td>9.8±6.7</td>
<td>10.9±6.6</td>
</tr>
<tr>
<td>MPAP</td>
<td>50.8±11.6</td>
<td>50.5±10.5</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; RVEDP, right ventricular end-diastolic pressure; MPAP, mean pulmonary artery pressure.

### Table 3. Echocardiographic Variables

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Before pericardiotomy</th>
<th>After pericardiotomy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular end-diastolic area, short-axis (cm²)</td>
<td>9.20±3.9</td>
<td>9.24±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic area, four-chamber (cm²)</td>
<td>15.3±5.9</td>
<td>15.5±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular end-diastolic area, four-chamber (cm²)</td>
<td>23.2±5.7</td>
<td>22.6±5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Right–to–left ventricular free wall end-diastolic diameter (cm)</td>
<td>7.9±1.0</td>
<td>7.9±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Right ventricular free wall–to–interventricular septum end-diastolic diameter (cm)</td>
<td>4.3±0.6</td>
<td>4.3±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Interventricular septum–to–left ventricular free wall end-diastolic diameter (cm)</td>
<td>2.7±0.9</td>
<td>2.6±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Eccentricity index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.7±0.4</td>
<td>1.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic</td>
<td>1.8±0.3</td>
<td>2.0±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Doppler mitral inflow indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early diastolic (E) velocity (cm/sec)</td>
<td>47±15</td>
<td>46±16</td>
<td>NS</td>
</tr>
<tr>
<td>Late diastolic (A) velocity (cm/sec)</td>
<td>55±18</td>
<td>56±14</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.95±0.45</td>
<td>0.89±0.35</td>
<td>NS</td>
</tr>
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</table>
We previously documented consistent and marked right-sided cardiac enlargement associated with chronic pulmonary thromboembolic disease in a population quite similar to that of the present study. In that report, mean end-systolic right atrial and end-diastolic right ventricular areas (by transthoracic echocardiography) in 30 patients with chronic thromboembolic pulmonary hypertension were $31 \pm 12$ and $33 \pm 7$ cm$^2$, respectively, compared with $14 \pm 4$ and $21 \pm 3$ cm$^2$ in normal controls ($p<0.001$ for both values).

Through echocardiographic measurements of cardiac area, the current study further demonstrates that total cardiac area, as well, was increased significantly in the study population. Thus, pericardial adaptations to chronic cardiac enlargement could be examined. In this investigation of 14 adults with chronic pulmonary thromboembolic disease, no hemodynamic or echocardiographic variable changed significantly after pericardial influence was removed by wide and complete pericardiectomy. This suggests that in humans with chronic right ventricular pressure overload and cardiac enlargement, the pericardium adapts, becomes more compliant, and maintains only minimal restraining effect on cardiac geometry; furthermore, the pericardium does not appear to be directly involved in the often severe interventricular septal deformations seen in this condition.

Comparisons With Previous Studies

Past studies have demonstrated the effect of the pericardium in acute volume overload both in animal models and in humans: there is little doubt that rapid increases in intrapericardial volume (either by cardiac enlargement or by pericardial effusion) can markedly enhance ventricular interactions and alter left ventricular filling characteristics. Freeman and LeWinter, using a canine model, found that the pericardium gradually increases in mass and compliance in response to chronic volume overload. Although it has been suggested that the human pericardium probably responds in a similar manner, there is no conclusive evidence to support this extrapolation.

The most direct studies on the human pericardium have been performed during open-heart surgery. In nine patients with normal left ventricular size and function, Lima et al. showed that the pericardium had no effect on septal geometry in the euvoletic state. Mangano et al. studied 15 patients undergoing coronary artery bypass surgery (all with normal left ventricular size) and found no significant changes in ventricular volume, pressure, and function (as measured by ejection fraction and cardiac index) immediately after pericardiectomy.

Boltwood et al. examined the effect of pericardial restraint in patients with normal cardiac size and in those with cardiomegaly caused by left-sided cardiac disease who were undergoing cardiac surgery. They measured pericardial and transmural pressures by using an intrapericardial catheter with a collapsible latex end balloon. In the group of subjects with cardiomegaly, as in the present study, there was no change in mean right atrial pressure, mean arterial and pulmonary artery pressures, heart rate, and cardiac index before and after pericardiectomy. Although mean transmural right atrial pressure and right ventricular stroke work index increased after pericardiectomy, no change was seen in mean transmural left ventricular filling pressure. The authors suggested that in patients with cardiomegaly, specifically those with right ventricular hypertrophy and dilation, sufficient chronic pericardial enlargement would take place, thereby allowing a sizable transmural diastolic pressure. They concluded that "the effect of hypertension on right ventricular free wall compliance may potentiate the elevation in transmural diastolic pressure allowed by pericardial enlargement."

Although the present study demonstrates no change in either right ventricular size or intracavitary pressures after pericardiectomy, intrapericardial pressures were not measured, and thus, it is not possible to assess changes in transmural right- and left-sided cardiac pressures. In general, however, the hemodynamic results of the present study confirm those of Boltwood et al. Additional data regarding the lack of change in right and left ventricular dimensions before and after pericardiectomy in a population with cardiomegaly caused purely by right ventricular pressure overload are consistent with chronic pericardial adaptation and enlargement.

Limitations

In the present study, ventricular volumes were not measured directly or calculated from echocardiographic parameters. Right ventricular volume is difficult to assess because of its geometry, which may be further distorted by pressure overload. Therefore, we have limited our analysis to interventricular septum-to-right ventricular free wall distance and four-chamber right ventricular end-diastolic area, which have been shown to correlate with changes in mean pulmonary artery pressure. Similarly, distortion of the left ventricular...
shape prevented us from using standard geometric equations for volume calculations. Thus, we have reported orthogonal area calculations and several left ventricular dimensions in lieu of possibly erroneous volume determinations. Given the lack of change in all of these parameters before and after pericardiotomy, it seems unlikely that any real changes in ventricular volume and geometry occurred.

Although intracardiac pressures are often measured from the level of the mid right atrium, pressure recordings in this study were performed with transducers zeroed at the level of the right ventricular free wall, because transducer placement at the level of the right atrium would have required fluid-filled catheters more than 6 in. long, causing unacceptable frequency damping of the pressure tracing. This method may underestimate left ventricular pressures slightly; however, the underestimation is consistent, and pressure differences before and after pericardiotomy are unaffected.

In patients with pulmonary hypertension, the absolute value of left ventricular eccentricity index measured by transesophageal echocardiography differs somewhat from that measured in thoracoscopic views, as the more oblique transesophageal imaging plane accentuates the eccentricity. This difference, however, is consistent in all patients studied; therefore, we believe comparisons of change in this index remain valid.

The effects of anesthesia and mechanical ventilation must also be considered. The study patients were anesthetized with intravenous fentanyl, a potent opioid agent. While many opiates have been associated with hypotension, bradycardia, and occasional hypertension during cardiovascular surgery, fentanyl rarely causes these problems and in most instances does not affect inotropic state, mean arterial pressure, cardiac output, or stroke volume.\(^{33,34}\) Positive-pressure ventilation, in general, causes a mild drop in cardiac output by decreasing venous return; this is usually promptly restored by intravenous fluids.\(^{35}\) All study patients were hemodynamically stable and at steady state during data collection at the time of pericardiotomy. Although hemodynamic variables in a given patient may differ somewhat between the conscious and anesthetized states, this effect does not alter the finding that these variables showed no significant change before and after pericardiotomy.

Finally, pericardial pressures were not directly recorded. The most accurate method for the measurement is controversial, and there is evidence that in the absence of a pericardial effusion, a simple fluid-filled catheter may significantly underestimate pericardial pressure.\(^{36}\) The insertion of a fluid-filled, flat intrapericardial balloon catheter was felt to be too time-consuming and technically demanding for inclusion in the protocol.

**Summary**

This study of patients with chronic, severe right ventricular pressure overload and cardiac enlargement demonstrates that the pericardium has little or no role in maintaining or influencing the often marked cardiac and septal distortions seen in this disease. In addition, this report extends previous animal studies and confirms that the human pericardium is a dynamic, adaptable structure capable of responding over time to changes in cardiac size and geometry.

**Acknowledgments**

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**References**

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