Ventricular Interaction During Experimental Acute Pulmonary Embolism

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Although stroke volume may decrease markedly after acute pulmonary embolism, left ventricular end-diastolic pressure (LVEDP) usually changes very little, which suggests that compliance or contractility or both are reduced. To test the hypothesis that the altered LV function during pulmonary embolism is primarily due to reduced preload mediated by increased pericardial constraint, hemodynamics and chamber dimensions (measured by sonomicrometry) were assessed in seven anesthetized dogs during control volume loading, after pulmonary embolism (with autologous blood clot), and after repeated pulmonary embolism in the volume-loaded state. The correlation between LVEDP and an index of LVED volume (LVED area index) throughout a wide range of LVEDP before and after embolism was weak (mean $r = 0.42$; range, 0.0–0.82). However, the correlation between transmural LVEDP (LVEDP – directly measured pericardial pressure) and LVED area index (mean $r = 0.78$; range, 0.61–0.94) was significantly higher ($p = 0.03$). Similarly, an index of stroke work (LV area stroke work) correlated less well ($p < 0.01$) with LVEDP (mean $r = 0.43$; range, 0.07–0.77) than with transmural LVEDP (mean $r = 0.82$; range, 0.68–0.92). LV area stroke work also correlated well with the LV area index (mean $r = 0.84$; range, 0.70–0.95). These data indicate that neither compliance nor contractility is substantially altered during acute pulmonary embolism. The altered LV performance is due to reduced LV preload as reflected by a decrease in transmural LVEDP. This study also demonstrates that LVEDP is a poor index of LV preload during pulmonary embolism, whereas transmural LVEDP accurately reflects LVED dimensions. (Circulation 1988;78:761–768)

Hemodynamic effects of acute pulmonary embolism include increased pulmonary artery and right ventricular (RV) pressures, and when embolism is severe, the effects include decreased cardiac output, systemic hypotension, and death. The reduction in stroke volume has been attributed to reduced left ventricular end-diastolic (LVED) volume. However, LV filling pressure is usually altered only slightly and may even increase, which suggests that pulmonary embolism may result in decreased LV compliance or contractility or both.

Based on earlier studies from our laboratory and from other laboratories, we hypothesized that acute pulmonary embolism would cause a reduction in LV stroke volume by reducing preload; this would occur because of an increase in pericardial constraint. We reasoned that as the RV dilates secondary to the increased afterload, pericardial pressure would also increase. In addition, the increase in RV end-diastolic pressure (RVEDP) and the decrease in LV diastolic filling would reduce the transseptal pressure gradient. Thus, true LV distending pressure (i.e., reflected by both transmural LVEDP and transseptal pressure gradient) would be considerably lower than indicated by intracavitary LVED measurement. To test this hypothesis, we studied animals in which pulmonary embolism was produced during control conditions and after the LVEDP was increased by volume loading. Changes in intracavitary and transmural LVEDP were correlated with indexes of LVED volume and systolic function. The results of this study demonstrate that intracavitary LVED measurements do not accurately reflect LVED volume during acute pulmonary embolism, that transmural LVED is a reliable index of LV volume, and that neither LV compliance nor contractility is substantially altered during pulmo-
inary embolism. Our results may also provide insight into the apparent paradox of LV failure in patients with acute pulmonary embolism.²⁻⁴,⁷

Materials and Methods

Animal Preparation

Seven dogs (weighing 20–24 kg) were anesthetized initially with 25 mg/kg i.v. sodium thiopental and subsequently with morphine only, which was first administered as a bolus (1 mg/kg i.v.) and then infused at a rate of 0.75 mg/kg/hr. Additional boluses and increased infusion rates were administered as necessary to maintain satisfactory anesthesia. The animals were ventilated with room air by a constant volume respirator (Model 607, Harvard Apparatus, Millis, Massachusetts). During instrumentation, boluses (100–200 ml) of heparinized Ringer’s lactate solution were infused to maintain normal aortic pressure. Autologous blood clot was prepared by adding 1,000 units thrombin to 100–150 ml freshly drawn blood, which was cut into approximately 0.5–1 cm³ portions before injection. A midline sternotomy was performed with the dog in the supine position. The ventral surface of the pericardium was incised transversely along the base of the heart, and the heart was removed from the pericardium during instrumentation. Two flat, liquid-containing balloons³ were sutured loosely to the epicardium; one was positioned on anterolateral surface of the LV, and the other was positioned over the middle of the RV. Septum-to-RV free wall, septum-to-LV free wall, and LV anteroposterior diameters were measured by sonomicrometry (Triton Technology, San Diego, California) as previously described.¹² The heart was repositioned in the pericardium, and the margins were reapproximated with several individual sutures. Care was taken to avoid decreasing pericardial volume. LV and RV pressures were measured with 8F micromanometer-tipped catheters with reference lumens (Model PR279, Millar Instruments, Houston, Texas) inserted through a carotid artery and internal jugular vein, respectively. Aortic and right atrial pressures were measured with fluid-filled catheters introduced through peripheral vessels. A single electrocardiogram lead was recorded. The chest was closed, and the animal was allowed to stabilize.

Conditioned signals (Model VR16, Electronics for Medicine, White Plains, New York) were acquired with a PDP-11/23 MINC computer. The analog signals were passed through antialiasing, low-pass filters with a cutoff frequency of 100 Hz and were then sampled at a frequency of 200 Hz. The digital data were subsequently analyzed on a VAX 11/750 computer (Digital Equipment, Maynard, Massachusetts).

Experimental Protocol

Hemodynamic and ultrasonic measurements were obtained continuously for 3 minutes during each intervention, each beginning with a 30-second control period. To establish preembolism (control) LV pressure-volume relations, the animals were rapidly volume-loaded to raise the LVEDP to approximately 30 mm Hg by infusing 300–600 ml heparinized Ringer’s lactate solution through a large-bore catheter into a femoral vein. Phlebotomy was used to reduce the LVEDP to the preinfusion level. The animals were allowed to stabilize; then pulmonary embolism was produced by injecting 5–10 clots suspended in residual unclotted blood through the femoral vein catheter. Intravenous fluid (200–400 ml) was then administered to increase and maintain the LVEDP above 20 mm Hg. Embolization was repeated at intervals of 5–10 minutes until aortic systolic pressure decreased to 80 mm Hg or less.

Data Analysis

Only data collected at end expiration were analyzed. Transmural LVEDP was calculated as intracavitary LVEDP – pericardial (balloon) pressure. The product of the LV minor-axis diameters (LV antero-posterior diameter × septum-to-LV free wall diameter) was used as an index of LV area and, hence, volume. LV area stroke work (fLVEDP pressure × LV area index × change in the LV area index × change in LV pressure) was used as an index of systolic function. End-diastolic transseptal pressure gradient was calculated from LVEDP – RVEDP. All of these diastolic and systolic relations include data obtained during control volume loading (preembolism) combined with those obtained during the subsequent interventions. Data were excluded when sudden hemodynamic deterioration occurred (aortic systolic pressure <50 mm Hg).

Statistical Analysis

Multiple linear regressions were performed to obtain correlation coefficients for the relations between both LVEDP and transmural LVEDP with LV area index and LV area stroke work as well as for the relation between LV area index and LV area stroke work in each dog. Student’s t test for paired data was used to compare the correlations between both LVEDP and transmural LVEDP with LV area index and LV area stroke work. Repeated measures analysis of variance was used to compare the pressure and dimension measurements obtained before and after embolism. A probability less than 0.05 was considered to be significant.

Results

Hemodynamic and Dimensional Changes

Table 1 lists the mean hemodynamic and dimension measurements obtained just before and after the first infusion of blood clot as well as just before and after the last embolization that did not result in severe hemodynamic deterioration. The increased RV and pericardial pressures present before the first embolization were attributed to the fact that the
**TABLE 1.** Hemodynamic and Dimensional Changes Due to Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>Before volume loading</th>
<th></th>
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<th></th>
<th>After volume loading</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before embolus</td>
<td>Embolus</td>
<td></td>
<td></td>
<td></td>
<td>Before embolus</td>
<td>Embolus</td>
</tr>
<tr>
<td>Peak RVSP (mm Hg)</td>
<td>38 ± 10</td>
<td>53 ± 6</td>
<td></td>
<td>&lt;0.05</td>
<td>56 ± 6</td>
<td>81 ± 11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>9 ± 1</td>
<td>11 ± 2</td>
<td></td>
<td>&lt;0.05</td>
<td>25 ± 3</td>
<td>26 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>7 ± 0.5</td>
<td>8 ± 0.6</td>
<td></td>
<td>&lt;0.01</td>
<td>20 ± 5</td>
<td>21 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial pressure over RV (mm Hg)</td>
<td>7 ± 1</td>
<td>9 ± 1</td>
<td></td>
<td>&lt;0.05</td>
<td>20 ± 7</td>
<td>18 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial pressure over LV (mm Hg)</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td></td>
<td>NS</td>
<td>17 ± 7</td>
<td>16 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak LVSP (mm Hg)</td>
<td>113 ± 6</td>
<td>106 ± 12</td>
<td></td>
<td>NS</td>
<td>125 ± 19</td>
<td>98 ± 21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9 ± 1</td>
<td>8 ± 2</td>
<td></td>
<td>&lt;0.05</td>
<td>24 ± 4</td>
<td>17 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Transmural LVEDP (mm Hg)</td>
<td>2 ± 1</td>
<td>2 ± 2</td>
<td></td>
<td>NS</td>
<td>7 ± 6</td>
<td>0 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Transseptal pressure gradient (mm Hg)</td>
<td>0 ± 1</td>
<td>-2 ± 2</td>
<td></td>
<td>NS</td>
<td>-1 ± 3</td>
<td>-8 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV anteroposterior diameter (mm)</td>
<td>63 ± 6</td>
<td>63 ± 6</td>
<td></td>
<td>NS</td>
<td>62 ± 6</td>
<td>61 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Septum-to-RV free wall diameter (mm)</td>
<td>28 ± 2</td>
<td>30 ± 3</td>
<td></td>
<td>&lt;0.05</td>
<td>35 ± 7</td>
<td>37 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Septum-to-LV free wall diameter (mm)</td>
<td>59 ± 16</td>
<td>57 ± 18</td>
<td></td>
<td>NS</td>
<td>52 ± 18</td>
<td>50 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVED area index (mm²)</td>
<td>3,719 ± 1,331</td>
<td>3,631 ± 1,415</td>
<td>NS</td>
<td></td>
<td>3,283 ± 1,364</td>
<td>3,107 ± 1,414</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV area stroke work* (mm Hg x mm²)</td>
<td>217 ± 78</td>
<td>174 ± 82</td>
<td></td>
<td>&lt;0.05</td>
<td>311 ± 130</td>
<td>181 ± 153</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Pre-embolus measurements were obtained just before embolization. Measurements after embolization were obtained at the time of maximum increase in right ventricular systolic pressure.

RV, right ventricular; LV, left ventricular; RVSP, RV systolic pressure; RVEDP, RV end-diastolic pressure; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; LVED area index, LV end-diastolic area index. NS, nonsignificant.

*LV area stroke work is the LV stroke work computed on the basis of the area index.

animals were still mildly volume expanded after control volume loading and phlebotomy. (Before control volume loading, mean peak RV systolic pressure was 32 mm Hg, and RA pressure and pericardial pressures over the RV and LV were 5, 5, and 6 mm Hg, respectively; the transseptal pressure gradient was 3 mm Hg, and the LV area was 3,050 mm².) As expected, RV systolic pressure increased significantly after embolism in both volume states. During the first embolization, there was a significant increase in RVEDP, right atrial pressure, and pericardial pressure over the RV; pericardial pressure over the LV did not change significantly. During the final embolization, these pressures were not altered significantly. LVEDP decreased significantly after embolism in both volume states. Transseptal pressure gradient decreased significantly after the last embolization, but the decrease in transmural LVEDP was not significant (p = 0.1) despite a decrease in all six dogs in which the measurements were available. Peak systolic LV pressure decreased significantly only with embolization in the volume-loaded state. Septum-to-RV free wall diameter increased significantly after the first embolization, but the increase after the final embolization was not statistically significant. However, the overall increase in diameter from before the first to the final embolization was significant (p < 0.01). The decrease in septum-to-LV free wall diameter was not significant after embolization at lower vascular volume but was after embolism at high LVEDP. LV anteroposterior diameter remained unchanged throughout the experiment. LVED area index decreased significantly only after embolization when LVEDP was elevated. Thus, embolization in the volume-loaded state caused a significant decrease in area index because of a leftward shift of the ventricular septum. This was associated with a significant decrease in LV area stroke work, which indicated a parallel decrease in systolic performance.

**Diastolic Function**

Figure 1 shows the LVED pressure-volume relations during control volume loading as well as after subsequent embolizations before and after volume expansion in a representative dog. Figure 2 shows
the data from the other six animals. As shown in Table 2, LVED area index correlated poorly with LVEDP (mean \( r=0.42 \); range, 0–0.82) but significantly better (\( p=0.03 \)) with transmural LVEDP (mean \( r=0.78 \); range, 0.61–0.94). As suggested in Figures 1 and 2 and by the close correlation between transmural LVEDP and area index during both control volume loading and the subsequent interventions (Table 2), there appears to be no systematic variation in compliance. Conversely, no consistent relation was apparent between LVEDP and area index during control volume loading and the subsequent interventions.

Systolic Function

As illustrated in Table 2 and Figures 3 and 4, LV area stroke work correlated poorly with LVEDP (mean \( r=0.43 \); range, 0.07–0.77). The correlation between area stroke work and transmural LVEDP (mean \( r=0.82 \); range, 0.74–0.92) was significantly better (\( p<0.01 \)). Area stroke work also correlated well with area index (mean \( r=0.84 \); range, 0.70–0.95). The LV area stroke work and transmural LVEDP and LV area stroke work and LV area index relations appeared similar during both control volume loading before embolism and the subsequent interventions, which suggests that there was no systematic variation in contractility. Conversely, no consistent LV area stroke work and LVEDP relation was apparent during control volume loading and the subsequent interventions.

Transseptal Pressure Gradient

There was a close relation between changes in the transseptal pressure gradient and changes in septum-to-RV and -LV free wall diameters, LV area index, and LV area stroke work regardless of the intervention (Table 2 and Figure 5). As the transseptal pressure gradient

<table>
<thead>
<tr>
<th>Dog</th>
<th>vs. LVEDP</th>
<th>vs. Transmural LVED</th>
<th>vs. Transmural pressure gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.32</td>
<td>0.94</td>
<td>0.88</td>
</tr>
<tr>
<td>2</td>
<td>0.57</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>0.82</td>
<td>0.69</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>0.28</td>
<td>0.61</td>
<td>0.81</td>
</tr>
<tr>
<td>5</td>
<td>0.00*</td>
<td>0.67</td>
<td>0.39</td>
</tr>
<tr>
<td>6</td>
<td>0.81</td>
<td>0.79</td>
<td>0.52</td>
</tr>
<tr>
<td>7</td>
<td>0.11</td>
<td>0.89</td>
<td>0.91</td>
</tr>
<tr>
<td>mean</td>
<td>0.42</td>
<td>0.78</td>
<td>0.75</td>
</tr>
</tbody>
</table>

\( p = 0.03 \)
pressure gradient became more negative, septum-to-LV free wall diameter and area index decreased, and septum-to-RV free wall diameter increased; the plotted shape of the relation suggests a limit to how far the septum can shift to the left.

Relation Between Right Atrial and Left Ventricular Pericardial Pressure

As shown in Figure 6, right atrial pressure closely reflected LV pericardial pressure in all seven animals; the correlation coefficients ranged from 0.91 to 0.98.

Discussion

The hemodynamic and dimensional changes observed during acute pulmonary embolism in this study are similar to those previously reported in acute pressure overload of the RV in experimental models\(^10-14,16,19,20,22\) and in patients.\(^1,3,4,9,15,17\) RV systolic pressure increased after each infusion of blood clot. LVEDP decreased significantly after embolization in both volume states. Pericardial pressure increased significantly only over the RV after the first embolization, whereas pericardial pressure over the LV did not change significantly. Right atrial pressure and RVEDP increased significantly only after the first embolization. This change is somewhat different from that observed in our earlier study\(^12\) in which severe pulmonary artery constriction was produced in normovolemic dogs; in that study, pericardial pressure over the RV increased, whereas it decreased over the LV. However, the intervention was very brief and relatively extreme; therefore, those results do not necessarily contradict the findings of the present study.

The hemodynamic changes were associated with a significant increase in septum-to-RV free wall diameter, a significant decrease in septum-to-LV free wall diameter (only after repeated embolism), and no significant change in the LV anteroposterior diameter; this is consistent with a leftward shift of the ventricular septum. As a result, there was a significant decrease in the LV area index (only
after repeated embolism) and LV area stroke work and only minor changes in LVEDP.

**Diastolic Function**

When the LV pressure-volume relation was plotted with intracavitary LVEDP, one would conclude that LV compliance decreased after pulmonary embolism. However, when transmural LVEDP was plotted against volume (Figures 1 and 2), no clear shift in the pressure-volume relation was evident. This was true throughout a wide range of intracavitary pressures (including volume loading before embolism, during embolization, and during subsequent volume loading), which suggests that there was no substantial change in myocardial compliance. Mirsky and Rankin23 have previously suggested that RVEDP should be included in the algorithm to calculate LV transmural pressure when considering LV pressure-volume relations. We have examined our data with respect to this suggestion and found no substantial difference in the results. This was expected because RVEDP and LV pericardial pressure were similar in all dogs.

The increase in septum-to-RV free wall diameter and decrease in the septum-to-LV free wall diameter is compatible with a leftward septal shift as a major factor accounting for the decrease in LV volume (because anteroposterior diameter did not change). The relations between the transseptal gradient and the septum-to-free wall diameters were generally curvilinear, implying there are physical limits to the degree of septal displacement that can occur in response to an altered transseptal gradient.24

We have no data describing the effects of a large positive transseptal gradient because the experiment was not designed to examine this portion of the relation. These results are similar to those we previously reported11 in experiments during pulmonary artery constriction, are similar to the studies of others,13,20,21 and are in general agreement with our current understanding of diastolic septal mechanics.25-27 The importance of the contribution of pericardial constraint to the mechanism of the shift has been emphasized previously; opening the pericardium results in less septal shift than occurs while the pericardium is intact.20,21,28

Our data differ from those in a recent report that concluded that septal shift was not an important factor in the reduction of LV volume in dogs with pulmonary vascular injury induced by glass beads.10 The degree of elevation of RV diastolic pressure in that study suggests that a septal shift was not observed because the increase in RV afterload was not as great as that produced by the repeated embolization in our study.

Right atrial pressure, which has been demonstrated to approximate pericardial pressure in previous studies29,30 and in this study (Figure 6), may become elevated in patients without preexisting cardiac disease who sustain acute pulmonary embolism. This suggests that pericardial pressure can increase secondary to pulmonary embolism even when LV filling pressure is normal. Certainly, volume loading in our animal model resulted in increased LVEDP despite a decrease in LV transmural pressure and LV area index. This observation may (at least in part) explain the occurrence of an elevated LV filling pressure after pulmonary embolism in humans.

**Systolic Function**

Stroke work correlated poorly with intracavitary LVEDP, whereas it correlated well with both transmural LVEDP and LV area index. Assuming that our index of LV minor axis area provides a reliable estimate of end-diastolic fiber length, the results indicate that contractility did not change in response to embolization and that the operation of the Frank-Starling mechanism is sufficient to explain the
observed changes in stroke work. This is indicated by the observed, close relation between LV volume and stroke work during both types of interventions and over a wide range of intracavitary pressures. Furthermore, this is supported by the absence of a systematic change in heart rate during the course of the experiments.

**Clinical Implications**

Because diastolic filling of the LV is a critical determinant of systolic performance in acute pulmonary embolism, a method that can be used reliably to estimate end-diastolic volume (LV preload) should prove useful in the management of hemodynamically unstable patients. However, as suggested recently by Jardin et al. and previously by Katz in 1955, the use of LVEDP or pulmonary capillary wedge pressure to either estimate end-diastolic volume or even a volume change may be misleading. Not only is the correlation between intracavitary LVEDP and LV volume poor, but changes in LV volume clearly may be associated with directionally opposite changes in end-diastolic pressure. Our data indicate that LVEDP volume can be reliably estimated by transmural LVEDP which, in turn, can be estimated by readily available measurements (pulmonary capillary wedge pressure—right atrial pressure). Although considerable controversy remains as to the best way to measure pericardial pressure, data from this study and our previous studies in animals and patients have demonstrated the similarity between right atrial and pericardial pressures. Thus, this approach may prove useful in the clinical monitoring of patients with pulmonary embolism.

In summary, this study indicates that the deterioration in LV performance during acute pulmonary embolism is due to diminished LV preload. Although changes in intracavitary LVEDP suggest that compliance or contractility or both decrease, it is evident when pericardial constraint and ventricular interdependence are taken into account that neither is substantially altered but that the reduced performance is due to impaired LV diastolic filling.

**References**


**KEY WORDS** • left ventricular function • right ventricular pressure overload • pericardial constraint • interventricular septum
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