Load Dependence of Left Ventricular Diastolic Pressure–Volume Relations During Short-term Coronary Artery Occlusion

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We evaluated the effect of altered loading conditions on left ventricular (LV) diastolic pressure–volume relations during acute coronary artery occlusion that was produced by inflation of an intracoronary balloon. Open-chest anesthetized dogs (n=18) were instrumented so that LV pressure (micromanometer) and LV volume (conductance) could be measured without disturbing the pericardium. The effects of brief periods of occlusion (1–2 minutes) were assessed under steady-state conditions before and after dextran infusion with the pericardium present and absent and during vena caval occlusion. Under steady-state conditions before dextran infusion with the pericardium removed, at an LV end-diastolic pressure (EDP) of 8.4±1.4 mm Hg, occlusion resulted in a rightward shift in the diastolic portion of the LV pressure–volume loop (ΔLVEDP, 2.7±2.3 mm Hg; ΔLVEDV, 6.3±4.7 ml, both p<0.05 versus control). After dextran infusion (LVEDP, 20.9±6.0 mm Hg), occlusion resulted in a rightward and upward shift in the diastolic portion of the LV pressure–volume loop (ΔLVEDP, 5.8±4.4 mm Hg; ΔLVEDV, 4.2±3.0 ml, both p<0.05 versus control). At low cardiac volumes before dextran infusion, the intact pericardium did not affect the response to occlusion. By contrast, after dextran infusion in the presence of an intact pericardium, LVEDP significantly increased (Δ, 6.4±3.6 mm Hg, p<0.05) but LVDEV did not (Δ, 0.7±1.5 ml, p=NS). There was a parallel upward shift in the diastolic portion of the LV pressure–volume loop that was eliminated by removal of the pericardium. Thus, the change in LV diastolic pressure and volume during occlusion varied and depended on the baseline cardiac volume and presence of the pericardium. Before dextran infusion with the pericardium present and absent, coronary artery occlusion did not alter the LV diastolic chamber stiffness parameter, which was calculated from the diastolic interval of an averaged steady-state beat (0.040±0.019 versus 0.036±0.015 mm Hg/ml, p=NS). After dextran infusion with the pericardium present and absent, coronary artery occlusion increased the LV diastolic chamber stiffness parameter (0.057±0.034 and 0.074±0.034 mm Hg/ml, both p<0.05 versus controls, respectively). Vena caval occlusion eliminated the shifts in the diastolic portion of the LV pressure–volume loop with the pericardium present and absent. In addition, the LV end-diastolic pressure–volume relation obtained by vena caval occlusion during occlusion with the pericardium present and absent was similar to that of the nonischemic LV. Thus, these data indicate that right ventricular and pericardial influences are responsible, in large part, for the shifts observed in the LV diastolic pressure–volume relations during acute coronary artery occlusion. In conclusion, the shift in position of the diastolic portion of the LV pressure–volume loop during coronary artery occlusion varies and is modulated by both the volume status of the LV and the pericardium. Despite these varying responses, the LV diastolic pressure–volume relations before and during acute coronary artery occlusion are similar when examined throughout the same LV pressure–volume range. (Circulation 1991;83:661–673)

Coronary artery occlusion produces abrupt contractile failure of the left ventricle (LV) resulting in decreased regional shortening and diminished pressure development. Early LV diastolic function is consistently impaired during coronary artery occlusion as evidenced by prolongation of the time constant of isovolumic relaxation. However, variable abnormalities have been observed in late or passive LV diastolic function. Early reports suggested that coronary artery occlusion results in a

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rightward shift of the diastolic portion of the LV pressure–segment length loop consistent with an increase in the distensibility of the ischemic segment. More recent studies have reported upward shifts of the diastolic portion of the LV pressure–volume loop during coronary artery occlusion consistent with a decrease in the distensibility of the LV. The mechanism and factors responsible for these varying results remain to be determined.

The rate and extent of relaxation, viscoelastic forces, and external factors including the right ventricle (RV), coronary vasculature, and pericardium can all affect the diastolic portion of the LV pressure–volume loop in the absence of ischemia. Moreover, these factors may be substantially affected during ischemia. Thus, it is difficult to identify whether a change in intrinsic myocardial diastolic stiffness or alteration of one of these other factors is responsible for a shift in the diastolic portion of the LV pressure–volume loop during coronary artery occlusion. Only limited data are available that examine the effect of external factors such as the pericardium on the shift in the diastolic portion of the LV pressure–volume loop during myocardial ischemia. In addition, because LV end-diastolic pressure determines the diastolic distensibility of the nonischemic LV, the end-diastolic pressure present before ischemia may substantially affect the interpretation of subsequent changes in LV diastolic chamber properties during ischemia. No systematic evaluation of the effect of the initial LV end-diastolic pressure on LV diastolic pressure–volume relations during acute coronary artery occlusion has been made.

To address these issues, we measured LV pressure and volume without disturbing the pericardium during coronary artery occlusion. With this model, the effects of acute coronary artery occlusion on LV diastolic pressure–volume relations were examined with and without the pericardium throughout a wide range of LV diastolic pressures and volumes.

**Methods**

**Instrumentation**

Eighteen adult mongrel dogs (weighing 20–30 kg) were premedicated with xylazine (1.0 mg/kg) and anesthetized with fentanyl hydrochloride and droperidol (Innovar–Vet, Pittman–Moore, Washington Crossing, N.J.). Pancuronium bromide (0.05 mg/kg) was also administered as an intravenous bolus at the beginning of instrumentation. Ventilation was provided with a Harvard volume respirator (Harvard Apparatus, South Natick, Mass.) and arterial blood gases were maintained within the physiological range. The chest was then opened by a midline sternotomy, and the lungs were retracted from the heart. The pericardiophragmatic ligament was left intact. Under fluoroscopic guidance, a micromanometer-tipped catheter was inserted into the right brachial artery (model MPC 500, Millar Instruments, Houston, Tex.) and advanced across the aortic valve into the LV. A similar catheter was placed in the RV through a left brachial vein. A 7F, 8-pole conductance catheter (Webster, Inc., Baldwin Park, Calif.) with a fluid-filled lumen was inserted into the left carotid artery and positioned in the apex of the LV. The distal electrode was placed at the apex, and the proximal electrode was placed just above the aortic valve under fluoroscopic visualization to ensure proper catheter positioning. A fluid-filled balloon-tipped catheter was inserted into the right brachial vein and was advanced into the RV to adjust the micromanometer-tipped catheter and was then advanced into the pulmonary artery. Care was taken to minimize blood loss during instrumentation, which was less than 10 ml in each case.

After instrumentation, the animals were given 3,000 units of heparin intravenously, which was supplemented with 1,000 units intravenously every 30 minutes to 1 hour. A coronary artery balloon occluder was placed in one of the coronary arteries with techniques that are routinely used to perform coronary angioplasty in patients. Briefly, the left coronary ostium was cannulated with a preformed 8F guiding catheter that was advanced under fluoroscopic guidance from the right femoral artery using small injections of a nonionic contrast agent (Omnipaque, Winthrop-Breon, N.Y.). A standard balloon dilatation system over a 0.014-in. guide wire was advanced in the guiding catheter and positioned within the proximal portion of either the left circumflex (n=10) or left anterior descending coronary artery (n=8). The guiding catheter was then pulled back into the aorta, and the balloon was left in a deflated condition in the coronary artery. The balloon and guide catheter were not moved during the remainder of the study. In each animal, the same coronary artery was used throughout the study. With this method, no measurable changes in hemodynamic function occurred with the balloon in a deflated position. In addition, no significant differences were observed in the hemodynamic response to occlusion of the left circumflex or anterior descending coronary arteries. Therefore, the results were pooled.

**Volume Measurements**

The conductance method used to measure LV volume is similar to the technique previously used in this laboratory. Briefly, an electrode catheter was inserted into the LV retrograde across the aortic valve and positioned in the apex of the LV under fluoroscopic guidance. Sensing electrodes that are evenly distributed along the catheter recorded conductances within the LV, which were then converted to LV volume by a signal conditioner (Sigma 5, Leycom, The Netherlands) with the following formula:

$$V(t)=\frac{1}{\alpha} L^2 \rho [G(t)-G_p]$$

where V(t) is measured LV volume at any time t, α is the empiric slope constant, L is distance between
sensing electrodes, $\rho$ is resistivity of blood that is inversely related to conductivity, $G(t)$ is sum of conductances measured within the LV cavity at any time $t$, and $G_p$ is parallel conductance. Both $L$ and $R$ were measured and entered into the signal conditioner. For the purposes of this study, $\alpha$ was assumed to be 1. Although $\alpha$ may vary from animal to animal, it should be relatively constant within any given animal under conditions such as were used in this study.\textsuperscript{19,21} At the current frequency used to generate the potential field (20 kHz at 0.04 mA), LV tissue, RV tissue and fluid, and the juxtapercardial tissues also contribute to the total measured conductance. This parallel conductance volume (volume offset) was calculated by transiently altering the conductance of the LV blood but not actual LV volume by injecting hypertonic saline (3–5 ml, 20% NaCl) into the pulmonary artery while simultaneously recording LV pressure and volume. This small volume of saline has negligible effects on LV function.\textsuperscript{19} Three saline calibrations were obtained and averaged at the beginning of the volume infusion and after its completion. At least 2 minutes separated each subsequent determination, and resistivity was measured before each saline calibration. The calculated offset was then subtracted from $V(t)$ to determine the absolute volume. This technique has been demonstrated to provide a reasonable estimate of the volume offset necessary to measure absolute LV volume.\textsuperscript{19,22–26} In this study, the parallel conductance volume was 57±22 ml and was not substantially altered by removing the pericardium (58±23 ml) or by dextran infusion (50±21 ml). In a subset of six animals, parallel conductance volume was similar before (59±15 ml) and during (58±11 ml) coronary artery occlusion.\textsuperscript{19} We\textsuperscript{19} and others\textsuperscript{27} have shown that the conductance catheter may underestimate the slope of the LV end-systolic pressure–volume relation during vena caval occlusion. However, the slope of LV end-diastolic pressure–volume indexes such as the stroke work–end-diastolic volume relation and $dP/dt_{\text{max}}$–end-diastolic volume relations were accurately measured by the conductance catheter.\textsuperscript{19} Thus, measurement of LV end-diastolic pressure–volume relations during vena caval occlusion, such as reported in this study, should be accurately obtained using the conductance catheter.\textsuperscript{21}

**Protocol**

**LV diastolic pressure–volume relations during steady state.** Steady-state baseline pressure and volume measurements were obtained at end expiration with the pericardium intact. The volume offset attributable to parallel conductance was determined with the hypertonic saline calibration technique. Metoprolol (0.1 mg/kg) was given intravenously to minimize the incidence of ventricular fibrillation during coronary artery occlusion. This dose does not result in complete $\beta$-adrenergic receptor blockade and is similar to the dose used in previous studies examining shifts in LV diastolic pressure–volume relations during ischemia.\textsuperscript{28–32} Metoprolol was not used in six of the animals. No substantial differences were observed in the results from these animals compared with those that received metoprolol. Thus, their results are pooled with those from the other animals.

The coronary artery balloon was then inflated to a pressure of 4 atm, and the coronary artery was occluded. Coronary artery occlusion was verified angiographically. Hemodynamic data were collected at steady state after 1–2 minutes of coronary artery occlusion. The same duration of occlusion was used throughout the study in any given animal. The balloon was quickly deflated, and the animal was allowed to recover for at least 10–15 minutes. In all cases, hemodynamic function returned to baseline within 1–2 minutes of balloon deflation. Previous data indicate that repeated coronary artery occlusions of brief duration (<5 minutes) do not cause cumulative depletion of myocardial high-energy phosphates.\textsuperscript{33} In addition, previous data from this laboratory indicate that transient coronary artery occlusion, such as used in this study, is reproducible and does not cause persistent measurable abnormalities in LV function.\textsuperscript{28,34}

With the pericardium still intact, dextran, which was adjusted to the same resistivity as the animals' blood, was infused until an LV end-diastolic pressure of approximately 20–30 mm Hg was obtained. Steady-state hemodynamics were measured after volume loading, and parallel conductance volume was then determined. The coronary artery balloon occluder was inflated, and hemodynamics were measured at steady state after 1–2 minutes of coronary artery occlusion. The balloon occluder was quickly deflated, and the animal was allowed to recover. After recovery, a volume of blood similar to the infusate volume was removed. The pericardium was then removed from the anterior and lateral aspects of the heart. The protocol outlined above was then repeated. In two animals, data were obtained only before dextran infusion with the pericardium present and absent, and in two animals, data were obtained only after dextran infusion with the pericardium present and absent.

**LV diastolic pressure–volume relations during vena caval occlusion.** Animals were instrumented as described earlier, and hemodynamics were allowed to stabilize. In addition, umbilical tape snares were placed around the superior and inferior venae cavae. With the pericardium intact, isoresistive dextran was infused until an LV end-diastolic pressure of approximately 20–30 mm Hg was obtained. Parallel conductance volume was assessed after dextran infusion by the hypertonic saline dilution method, and the animals were allowed to recover. Transient and rapid vena caval occlusion was then obtained with the umbilical tape snares. The vena caval occlusion was released when LV end-diastolic pressure was less than 10 mm Hg or when LV end-systolic pressure was less than 60 mm Hg. At least two vena caval occlusions were performed at each step of the protocol. After recovery, the coronary artery balloon occluder
Before Dextran Control Dextran Occlusion After Dextran Control Dextran Occlusion

![Graph showing LV pressure and volume](image)

**FIGURE 1.** Representative analog recordings showing left ventricular pressure (LVP), left ventricular dP/dt, and left ventricular volume (LVP) at control and during coronary artery occlusion before and after volume loading with dextran in one animal with the pericardium present. Before dextran infusion, coronary artery occlusion resulted predominantly in an increase in left ventricular volume. After dextran infusion, coronary artery occlusion resulted in an increase in left ventricular end-diastolic pressure without a significant increase in left ventricular end-diastolic volume.

was inflated, and the coronary artery was occluded. Completeness of occlusion was verified angiographically. At steady state after 1–2 minutes of coronary artery occlusion, hemodynamics were measured. Transient vena caval occlusion was then performed as described earlier. Both the coronary and vena caval occlusions were released, and the animal was allowed to recover. The pericardium was then re-covered. LV pressure, volume, and the protocol was then repeated.

The studies were performed in a laboratory accredited by the American Association for Accreditation of Laboratory Animal Care, with an experimental protocol that had been reviewed and approved by the institutional animal care and use committee.

**Data Analysis**

Data were collected for 15 seconds and digitized at 200 Hz. All collections were obtained during end expiration with the respirator off. Data were stored on a computer (286 AT, Dell Computer, Austin, Tex.) and analyzed with software developed in our laboratory. End diastole was defined as the relative minima of LV pressure after the A wave. End systole was defined as occurring at the point where the ratio between LV pressure and volume was maximal. LV diastolic pressure–volume curves were constructed by plotting LV pressure against the corresponding LV volume corrected for parallel conductance.

Hemodynamics were evaluated under steady-state conditions by averaging the collected beats. A minimum of five normal sinus beats were averaged in all of the analyses. In most cases, all beats collected during the 15-second recording period were averaged. Extrasystolic beats and postextrasystolic beats were excluded. LV dynamic diastolic chamber stiffness was calculated from LV pressure and volume points from minimal LV diastolic pressure to the peak of the A wave from a steady-state-averaged beat by a simple monoexponential function: $P = a e^{\beta V}$, where $P$ is LV pressure, $V$ is LV volume, $a$ is pressure axis intercept at 0 volume, and $\beta$ is LV diastolic chamber stiffness. Points less than an LV pressure of 5 mm Hg were excluded from analysis because the LV diastolic pressure–volume relation is not monoexponential at extremely low pressures and volumes. This analysis integrates the viscous effects of early rapid filling and atrial contraction with passive chamber properties and, therefore, may not purely reflect passive chamber stiffness. In addition, it assumes a monoexponential relation between pressure and volume that may not exist throughout the entire range of values studied. However, it provides a commonly used index of LV diastolic chamber stiffness. The LV end-diastolic pressure and volume points obtained during vena caval occlusion were also fit to the simple monoexponential function.

**Statistical Analysis**

All data are expressed as mean±SD. Comparisons were analyzed by paired $t$ tests with Bonferroni’s correction for multiple comparisons. A probability of less than 0.05 was considered significant.

**Results**

**Steady State**

A representative analog recording showing LV pressure and volume in an animal with an intact pericardium before and after balloon occlusion of a coronary artery is shown in Figure 1. Before dextran infusion, coronary artery occlusion resulted in a
TABLE 1. Steady-State Hemodynamics at Control and During Coronary Artery Occlusion Before and After Dextran Infusion With the Pericardium Present and Absent

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>RVP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>+dP/dtmax (mm Hg/sec)</th>
<th>LVEDV (ml)</th>
<th>LVESV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control before dextran</td>
<td>97±12</td>
<td>124±17</td>
<td>8.1±2.3</td>
<td>30±6</td>
<td>4.5±1.6</td>
<td>1,353±602</td>
<td>36±15</td>
<td>17±11</td>
</tr>
<tr>
<td>Occlusion</td>
<td>104±25</td>
<td>112±16*</td>
<td>10.7±2.3*</td>
<td>28±4</td>
<td>4.5±1.7</td>
<td>1,019±501*</td>
<td>43±17*</td>
<td>26±12*</td>
</tr>
<tr>
<td>Control after dextran</td>
<td>95±18</td>
<td>124±13</td>
<td>8.4±1.4</td>
<td>32±6</td>
<td>4.2±1.0</td>
<td>1,441±686</td>
<td>38±11</td>
<td>18±9</td>
</tr>
<tr>
<td>Occlusion</td>
<td>97±17</td>
<td>112±15*</td>
<td>11.1±2.9*</td>
<td>30±5</td>
<td>4.3±1.3</td>
<td>1,122±496*</td>
<td>45±12*</td>
<td>27±11*</td>
</tr>
</tbody>
</table>

Values are mean±SD.

HR, heart rate; LVP, peak left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; RVP, peak right ventricular pressure; RVEDP, right ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

*p<0.05 vs. control; †p<0.05 vs. pericardium present.

The diastolic portion of the LV pressure–volume loop from averaged cardiac cycles under control conditions and during coronary artery occlusion before and after dextran infusions are shown in Figure 2. Coronary artery occlusion resulted in similar small increases in LV end-diastolic pressure before dextran infusion with the pericardium present (Δ, 2.7±1.3 mm Hg, p<0.05) and with the pericardium absent (Δ, 2.7±2.3 mm Hg, p<0.05; p=NS versus pericardium present). There were equivalent large increases in LV end-diastolic volume with the pericardium intact (Δ, 7.6±4.1 ml, p<0.05) and with the pericardium absent (Δ, 6.3±4.7 ml, p<0.05, p=NS versus pericardium present). After dextran infusion, coronary artery occlusion resulted in similar large increases in LV end-diastolic pressure with the pericardium intact (Δ, 6.4±3.6 mm Hg, p<0.05) and with the pericardium absent (Δ, 5.8±4.4 mm Hg, p<0.05, p=NS versus pericardium present). By contrast, there were significant differences in the change in LV end-diastolic volume during ischemia after dextran infusion. There was no significant change in LV end-diastolic volume during coronary artery occlusion with the pericardium intact (Δ, 0.7±1.7 ml, p=NS), whereas there was a significant increase in LV end-diastolic volume with the pericardium absent (Δ, 4.2±3.0 ml, p<0.05; p<0.05 versus pericardium present).

The diastolic portion of the LV pressure–volume loop during coronary artery occlusion before and after dextran infusions are shown in Figures 3 and 4. Before dextran infusion, there was a rightward shift of the diastolic portion of the LV pressure–volume loop during coronary artery occlusion with the pericardium present and absent (Figure 3). However, after dextran infusion, the same balloon occlusion resulted in a parallel upward shift of the loop with the pericardium intact. After removal of the pericardium, the parallel upward shift during...
coronary artery occlusion was eliminated (Figure 4). Thus, variable shifts in the position of the diastolic portion of the LV pressure-volume loop were observed during coronary artery occlusion depending on the loading conditions present before the occlusion. Because the upward shift in the position of the LV end-diastolic pressure and LV end-diastolic volume as a consequence of coronary artery occlusion with the pericardium present (Per+) and absent (Per−) before (Dex−) and after (Dex+) volume loading with dextran. Before dextran, coronary artery occlusion resulted predominantly in an increase in LV end-diastolic volume similarly with the pericardium present or absent. After dextran, there was no significant increase in LV end-diastolic volume during coronary artery occlusion with the pericardium intact despite a significant increase in LV end-diastolic pressure. By contrast, both LV end-diastolic volume and pressure increased substantially during coronary artery occlusion with the pericardium removed.

**Before Dextran**

![Figure 3. Representative diastolic portions of left ventricular (LV) pressure-volume loops from averaged beats at control and during coronary artery occlusion before dextran infusion with the pericardium present and absent. In all of the animals, there was a rightward shift of the diastolic portion of the LV pressure-volume loop as a result of coronary artery occlusion. There were no significant differences in the shift of the loop with the pericardium present or absent.](image-url)

**Figure 2.** Scattergram comparing paired change in group mean left ventricular (LV) end-diastolic pressure and LV end-diastolic volume as a consequence of coronary artery occlusion with the pericardium present (Per+) and absent (Per−) before (Dex−) and after (Dex+) volume loading with dextran. Before dextran, coronary artery occlusion resulted predominantly in an increase in LV end-diastolic volume similarly with the pericardium present or absent. After dextran, there was no significant increase in LV end-diastolic volume during coronary artery occlusion with the pericardium intact despite a significant increase in LV end-diastolic pressure. By contrast, both LV end-diastolic volume and pressure increased substantially during coronary artery occlusion with the pericardium removed.
After Dextran

Figure 4. Representative diastolic portion of left ventricular (LV) pressure–volume loops from averaged beats at control and during coronary artery occlusion after dextran infusion with the pericardium present and absent. In all of the animals with the pericardium present, coronary artery occlusion resulted in an upward shift of the diastolic portion of the LV pressure–volume loop. After removal of the pericardium, the upward shift was abolished, and the same coronary artery occlusion resulted in a predominantly rightward and upward shift of the loop.

diastolic portion of the LV pressure–volume loop was eliminated by removal of the pericardium, the upward shift may be due, in large part, to pericardial restraint.

Results of fitting the diastolic interval of an averaged steady-state beat to a monoexponential function during the study are shown in Table 2. Before dextran infusion with the pericardium intact, coronary artery occlusion did not significantly alter the LV pressure axis intercept (2.92±1.56 versus 2.73±1.74 mm Hg, p=NS) or the LV diastolic chamber stiffness parameter (0.040±0.019 versus 0.036±0.015 mm Hg/ml, p=NS). Similar results were observed with the pericardium absent. After dextran infusion, coronary artery occlusion resulted in a significant increase in the LV diastolic chamber stiffness parameter with the pericardium present (0.041±0.023 versus 0.057±0.034 mm Hg/ml, p<0.05) and absent (0.054±0.025 versus 0.074±0.034 mm Hg/ml, p<0.05). Although the LV pressure axis intercept was larger with the pericardium present than with the pericardium absent, it was not signifi-

Table 2. Left Ventricular Diastolic Chamber Stiffness Analysis During Steady State

<table>
<thead>
<tr>
<th></th>
<th>Before dextran</th>
<th>After dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pericardium present</td>
<td>Pericardium absent</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Occlusion</td>
</tr>
<tr>
<td>( \alpha ) (mm Hg/ml)</td>
<td>2.92±1.56</td>
<td>2.73±1.74</td>
</tr>
<tr>
<td>( \beta ) (mm Hg/ml)</td>
<td>0.036±0.015</td>
<td>0.040±0.019</td>
</tr>
</tbody>
</table>

Values are mean±SD. LV pressure and volume points from minimum left ventricular diastolic pressure to the peak of the A wave of an averaged steady-state beat were used in this chamber stiffness analysis.

\( \alpha \), Left ventricular diastolic pressure intercept; \( \beta \), dynamic left ventricular chamber diastolic stiffness parameter.

\( *p<0.05 \) vs. pericardium present; \( \dagger p<0.05 \) vs. control.
The LV end-diastolic pressure–volume relations before and during coronary artery occlusion were evaluated by comparing the LV end-diastolic pressure–volume relations obtained during vena caval occlusion. LV end-diastolic pressure–volume points obtained by vena caval occlusion after dextran infusion under control conditions and during coronary artery occlusion with the pericardium present and absent are shown in Figure 7. LV end-diastolic pressure–volume points obtained from caval occlusion during coronary artery occlusion and from the nonischemic LV fell on the same LV end-diastolic pressure–volume relation. Similar results were observed with the pericardium present and absent. The results of the monoexponential fit of the LV end-diastolic pressure–volume relations are shown in Table 3. With the pericardium present, the LV pressure axis intercept was equivalent before and during (3.63±0.44 versus 2.66±0.25 mm Hg, p=NS) coronary artery occlusion. Similarly, the LV diastolic chamber stiffness parameter was not altered by coronary artery occlusion (0.040±0.007 versus 0.042±0.004 mm Hg/ml, p=NS). Coronary artery occlusion also did not substantially alter either the LV pressure axis intercept or the LV diastolic chamber stiffness parameter with the pericardium absent. Thus, these data suggest that the shifts in position of the LV end-diastolic pressure–volume points obtained during coronary artery occlusion are similar to the changes in the LV end-diastolic pressure–volume position obtained by passive filling of the nonischemic LV throughout the same LV pressure and volume range.

**Discussion**

We found that the effect of coronary artery occlusion on the shift of the diastolic portion of the LV pressure–volume loop varied and depended on several factors. At smaller LV volumes, coronary artery occlusion resulted in a rightward shift of the diastolic portion of the LV pressure–volume loop along the flat portion of the passive LV diastolic pressure–volume curve. This occurred whether the pericardium was present or absent. After dextran infusion had increased the LV volume, the same coronary artery occlusion resulted in a predominantly upward shift of the diastolic portion of the LV pressure–volume loop in the presence of the pericardium. This upward shift was eliminated by removing the pericardium and by vena caval occlusion, suggesting that both RV and pericardial factors were, in large part, responsible for the upward shift.

Our data also indicate that calculation of the LV diastolic chamber stiffness during coronary artery occlusion from the diastolic interval of a single beat can be significantly influenced by the LV diastolic pressure and volume range throughout which the data are obtained. Under steady-state conditions before dextran infusion, neither the LV pressure intercept nor the LV diastolic chamber stiffness parameter was altered by coronary artery occlusion.

**Vena Caval Occlusion**

We evaluated the effects of coronary artery occlusion on the LV diastolic pressure–volume relation during vena caval occlusion. The results from one animal of vena caval occlusion during coronary artery occlusion after dextran infusion with the pericardium intact are shown in Figure 5. Vena caval occlusion eliminated the parallel upward shift in the diastolic portion of the LV pressure–volume loop resulting from coronary artery occlusion. This occurred before a significant change in LV volume was observed, suggesting that RV and pericardial factors were responsible for the parallel upward shift of the diastolic portion of the LV pressure–volume loop observed in this animal. Beats obtained during vena caval occlusion under control conditions and during coronary artery occlusion were compared at a comparable LV diastolic pressure and volume. The results with the pericardium present and absent are shown in Figure 6. In each animal, the shift in the diastolic portion of the LV pressure–volume loop during coronary artery occlusion was eliminated by vena caval occlusion. This occurred similarly with the pericardium present and absent. As can be seen, the diastolic portions of the LV pressure–volume loops before and during coronary artery occlusion were superimposable when examined throughout the same pressure–volume range. This suggests that the apparent alteration in LV diastolic chamber properties occurring during coronary artery occlusion is due, in large part, to factors external to the LV.

**Note:**

Significantly altered by coronary artery occlusion according to this method of analysis.
By contrast, after dextran infusion, the LV diastolic chamber stiffness parameter increased during coronary artery occlusion with the pericardium present and absent. Because the coronary artery was occluded at the same site before and after dextran infusion and for the same length of time, the difference in LV diastolic chamber stiffness was probably not a result of differences in the severity of the ischemia elicited by the coronary artery occlusion. Instead, our data suggest that the steady-state LV diastolic chamber stiffness parameters obtained during coronary artery occlusion were substantially affected by the loading conditions of the LV present before ischemia. Data obtained during vena caval occlusion support this conclusion. When beats obtained by vena caval occlusion under control conditions and during coronary artery occlusion were compared throughout the same LV diastolic pressure and volume range, no significant differences occurred in the position and shape of the diastolic portions of the LV pressure–volume loops (Figure 6). Moreover, the position and shape of the LV end-diastolic pressure–volume relations under control conditions and during coronary artery occlusion were equivalent (Figure 7). Thus, the increase in LV diastolic chamber stiffness during coronary artery occlusion was similar to that of the nonischemic LV examined throughout the same LV diastolic pressure–volume range.

Only limited previous data are available that examine the effect of the pericardium on the response to acute coronary artery occlusion. Smiseth et al\textsuperscript{17} produced acute global LV ischemia failure in anesthetized dogs with microsphere embolization of the coronary arteries. Significant upward shifts were seen in the LV intracavitary end-diastolic pressure–volume relations during ischemic failure with the pericardium present but not in the transmural LV end-diastolic pressure–volume relation. They concluded that the pericardium mediated the upward shift in the LV end-diastolic pressure–volume relation and that global ischemia was not associated with consistent changes in myocardial compliance. Because the pericardium was opened and then resutured after placement of a pericardial balloon, pericardial effects may have been exaggerated in their study. However, the results from this study support their findings.
Vena Caval Occlusion

In addition, no previous study has systematically evaluated the effect of volume loading and altered loading conditions on the response to acute coronary artery occlusion. Two studies have examined the effect of vena caval occlusion on the LV diastolic pressure–volume relation during acute coronary artery occlusion. Hess et al. evaluated the effect of partial and complete acute coronary artery occlusion on the LV diastolic pressure–volume relation in the conscious dog. Complete, but not partial, coronary artery occlusion caused an upward shift in the position of diastolic portion of the LV pressure–volume loop. Inferior vena caval occlusion eliminated the upward shift, possibly as a result of decreased ventricular interaction from decreased RV pressure and volume. Although the pericardium was left open in their study, a fibrotic growth covers the LV in dogs that have undergone long-term instrumentation that may have acted as an external constraint similar to the pericardium. Most recently, Kass et al. investigated the effect of acute coronary artery occlusion on the LV diastolic pressure–volume relation in patients

![Diagram of Vena Caval Occlusion](image)

**Figure 7.** Left ventricular (LV) end-diastolic pressure–volume points obtained during vena caval occlusion after dextran infusion with the pericardium present and absent under control conditions and during coronary artery occlusion. In each animal, the LV end-diastolic pressure–volume relation obtained by vena caval occlusion before and during coronary artery occlusion had a similar position and shape. □ Control, pericardium present; ■, coronary artery occlusion, pericardium present; △, control, pericardium absent; ■, coronary artery occlusion, pericardium absent.

**Table 3. Left Ventricular End-Diastolic Chamber Stiffness Analysis During Vena Caval Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>Pericardium present</th>
<th>Pericardium absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Occlusion</td>
</tr>
<tr>
<td>$\alpha$ (mm Hg)</td>
<td>3.63±0.44</td>
<td>2.66±0.25</td>
</tr>
<tr>
<td>$\beta$ (mm Hg/ml)</td>
<td>0.040±0.007</td>
<td>0.042±0.004</td>
</tr>
</tbody>
</table>

Values are mean±SD. Left ventricular end-diastolic pressure and volume points obtained during vena caval occlusion were used in this chamber stiffness analysis.

$\alpha$, Left ventricular end-diastolic pressure intercept; $\beta$, static left ventricular end-diastolic chamber stiffness parameter.

*p<0.05 vs. pericardium present.
undergoing angioplasty. They observed an upward shift in the diastolic portion of the LV pressure-volume relation and an increase in LV diastolic chamber stiffness (single beat) during angioplasty. Similar to our findings, they also observed that the LV end-diastolic pressure-volume relation obtained by vena caval occlusion during coronary artery occlusion was similar to that obtained in the absence of ischemia. These data, in conjunction with data from the present study, suggest that altered loading conditions and external factors can substantially affect the position of the diastolic portion of the LV pressure-volume loop.

The mechanical alterations during obstruction of coronary blood flow have been extensively evaluated. The primary LV systolic disturbance during complete flow interruption is abrupt contractile failure resulting in a diminished pressure development, decreased regional shortening, and decreased cardiac output. Although Tennant and Wiggers first described the phenomenon of LV systolic bulging during coronary artery occlusion in 1935, there has not been a consensus on the effects of ischemia on LV diastolic function.

Although isovolumic relaxation and LV diastolic pressures both increase during ischemia, the reported effects of coronary artery occlusion on the LV diastolic pressure-volume relation have varied. LV diastolic distensibility has been shown to increase during experimental myocardial infarction but not change in the isolated LV during mild global ischemia. By contrast, recent studies showed a decrease in LV diastolic distensibility during acute experimental coronary artery occlusion and angioplasty. A substantial amount of the variability in past studies can be attributed to the tremendous heterogeneity in the study models of ischemia used to investigate the passive diastolic properties of the LV. Palacios et al. and Smiseth et al. examined the effects of global ischemia, whereas other studies evaluated the effects of occlusion of a single coronary artery. The duration of ischemia varied in the previous studies from 20 to 50 seconds to 6 hours. During the more prolonged periods of flow limitation, myocardial “creep” may have occurred, altering the LV diastolic chamber stiffness observed during an earlier period of flow obstruction. Thus, these different results may reflect differences in study conditions and, therefore, may not be comparable.

The findings from the present study may provide a basis for reconciling the varied results obtained in previous studies examining the effects of acute coronary artery occlusion. Studies reporting a rightward shift of the LV diastolic pressure-volume relation during acute coronary artery occlusion were performed in animals with the pericardium removed. Similarly, we observed a rightward shift in the LV diastolic pressure-volume relation in the absence of the restraining effect of the pericardium and at smaller LV volumes operating on the flat portion of the LV diastolic pressure-volume relation. By contrast, studies reporting an upward shift of the LV diastolic pressure-volume relation have been conducted in patients undergoing angioplasty, who had intact pericardia and who often had elevated resting LV end-diastolic pressures. Our data suggest that coronary artery occlusion obtained in the presence of pericardial restraint, or obtained with the LV operating on the steep portion of the LV diastolic pressure-volume relation, produces an increase in diastolic pressure. Because LV diastolic volume under these conditions changes little, the resultant shift in the diastolic portion of the LV pressure-volume loop is upward. Thus, the presence or absence of the pericardium and loading conditions of the LV present before coronary artery occlusion may substantially affect the response to acute coronary artery occlusion.

Clinical Implications

The difficulties inherent in extrapolating the effect of acute coronary artery occlusion on passive myocardial properties from shifts in the LV diastolic pressure-volume loop are evident from this study. An upward shift of the diastolic portion of the LV pressure-volume loop, such as occurs during “demand” ischemia, can be a result of increased myocardial stiffness. However, as we show in this study, pericardial restraint of LV filling may cause a similar type of upward shift. Thus, in clinical studies, a thorough understanding of the loading conditions present before coronary artery occlusion is important to appropriately interpret the data obtained during coronary artery occlusion. Ideally, investigations that evaluate the shifts in the diastolic portion of the LV pressure-volume loop during coronary artery occlusion should examine the passive properties of the nonischemic LV throughout a similar range of loading conditions.

Limitations of the Study

There are certain potential limitations of the study that merit discussion. First, the results of this study were obtained during the early phase of coronary artery occlusion and should not be extrapolated to longer occlusions when both myocardial and pericardial creep may influence the LV diastolic pressure-volume relation. Second, these results should not be extrapolated to conditions in which myocardial ischemia results from myocardial oxygen demand in excess of supply. Several previous studies showed that this form of ischemia alters the intrinsic diastolic stiffness of the LV independent of the effects of the pericardium and RV. Third, we analyzed the effect of regional ischemia on global parameters of LV diastolic chamber properties. Local changes in stiffness may have occurred that were not measured in this study. Last, we did not observe an increase in RV end-diastolic pressure during coronary artery occlusion after dextran infusion in the presence of the pericardium despite a parallel upward shift in the diastolic portion of the LV pressure-volume loop. Because we
did not directly measure pericardial pressure, we cannot conclusively state that the upward shift in the diastolic portion of the LV pressure–volume relation was entirely due to an increase in pericardial pressure. However, this type of shift only occurred in the presence of the pericardium and was eliminated by removal of the pericardium. Recent data indicate that pericardial pressure is not uniformly distributed over the heart. The lack of a change in RV end-diastolic pressure may be a manifestation of this phenomenon. Further studies will be necessary to evaluate this finding.

Summary

In this study, we observed that the shift in the position of the diastolic portion of the LV pressure–volume loop during acute coronary artery occlusion depended on the initial loading conditions of the LV. Changes in LV diastolic pressure–volume relations during coronary artery occlusion were similar to changes seen during passive filling of the nonischemic LV. These data suggest that clinical studies should consider the contribution of both the initial position of the LV on the LV diastolic pressure–volume curve and potential external pericardial restraint when evaluating shifts in the position of the diastolic portion of the LV pressure–volume loop during coronary artery occlusion.

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References

22. Hugenholtz PG, Serruys PW, Velde J, Kerkhof PLM, Moene RJ, Van Dijk AD, Van Der Velde ET, Koops B: Continuous stroke volume and cardiac output from intraventricular dimensions obtained with impedance catheter. Cardiol Res 1981;15:328–334
29. Serizawa T, Carabello BA, Grossman W: Effect of pacing-induced ischemia on left ventricular diastolic pressure-volume

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