Acute Decrease in Left Ventricular Diastolic Chamber Distensibility During Simulated Angina in Isolated Hearts

Shogen Isoyama, Carl S. Apstein, Laura F. Wexler, William N. Grice, and Beverly H. Lorell

It is not clear what factors contribute to the prompt and reversible decrease in left ventricular diastolic chamber distensibility during angina pectoris that is induced by an increase in myocardial energy demand due to exercise or pacing tachycardia. To simulate the demand ischemia that occurs clinically during pacing-induced angina, we used isolated, blood-perfused rabbit hearts with restricted coronary flow and increased myocardial energy demand. A constant left ventricular balloon volume model was used to measure left ventricular diastolic chamber distensibility during 6 minutes of low-flow global ischemia, induced by a reduction in coronary perfusion pressure from 100 to 20 mm Hg. To investigate the influence of different levels of myocardial energy demand, the effects of two different heart rates were studied during low-flow global ischemia; pacing tachycardia (6.4 ± 0.2 Hz, n = 7) was compared with the rabbit’s baseline heart rate of 4 Hz (n = 7). Low-flow ischemia caused a marked decrease in contractile function relative to the baseline preischemic state. In the pacing-tachycardia group, myocardial energy demand, as estimated by the rate × systolic pressure product, was significantly greater than in the constant heart-rate group. When tachycardia was imposed during low-flow global ischemia, there was a transient and reversible increase in insonolument left ventricular end-diastolic pressure from 14 ± 1 to 25 ± 4 mm Hg (measured during long diastoles obtained with transient cessation of pacing) in the pacing-tachycardia group, but there was no increase in left ventricular end-diastolic pressure during low flow ischemia in the constant heart-rate group with lower energy demand (p<0.01). The time constant of left ventricular relaxation also markedly increased in low-flow ischemia combined with pacing tachycardia. Glycolytic flux (as estimated by coronary venous-arterial lactate concentration difference) increased during low-flow ischemia at the baseline heart rate of 4 Hz but did not increase further during the elevated energy demand of pacing tachycardia. We conclude that in isolated, blood-perfused hearts, global myocardial ischemia due to a reduction in coronary flow alone is not associated with a decrease in diastolic chamber distensibility. However, when a pacing-induced increase in myocardial energy demand is superimposed on the ischemic myocardium and exceeds its capacity to generate high-energy phosphates, a rapid and reversible decrease in left ventricular diastolic chamber distensibility develops similar to that which occurs in response to pacing-induced angina in humans. This finding in isolated, blood-perfused hearts with global ischemia supports the hypothesis that the increase in left ventricular diastolic pressure that occurs during angina in humans is related to the effects of demand ischemia on myocardial relaxation per se and does not require dyssynchronous contraction of ischemic and nonischemic segments, nor does it depend on pericardial or right ventricular factors. (Circulation Research 1987;61:925–933)

In patients with coronary stenoses, substantial increases in left ventricular (LV) diastolic pressure relative to volume occur within minutes of the onset of angina pectoris that has been induced by an increase in myocardial energy demand due to exercise or pacing tachycardia.1-3 Furthermore, prompt and reversible decreases in diastolic chamber distensibility, as defined by the LV diastolic pressure-volume relation and pressure-segment length relation, have been also shown in open-chest dogs with coronary stenoses and regional ischemia induced by pacing tachycardia.10,11 The mechanisms responsible for this prompt, reversible impairment of LV diastolic function during clinical or experimentally simulated angina are controversial. Several explanations have been proposed: 1) right ventricular loading that can alter LV diastolic properties by means of “ventricular interaction” with or without an intact pericardium12-14, 2) dyssynchrony of the strength and duration of contraction in adjacent ischemic and nonischemic regions of myocardium, which can decrease LV chamber distensibility15-17, and 3) a direct effect of ischemia to acutely impair myocardial relaxation per se and thereby decrease diastolic chamber distensibility.18,19

The conclusion that acute ischemia can directly impair myocardial relaxation and thereby decrease chamber distensibility has remained controversial be-
cause several studies of isolated heart muscle have shown the opposite effect, i.e., an initial increase in LV chamber distensibility during acute ischemia. However, these studies have been performed in the context of "primary" or "supply ischemia," i.e., a reduction in coronary flow, without an increase in myocardial energy demand such as occurs during angina in humans. For example, primary low-flow ischemia did not produce a decrease in diastolic chamber distensibility in the early phase of ischemia in dog hearts,11,20-22 or in isolated rat or rabbit hearts perfused with Krebs-Henseleit buffer.18,23-25

We hypothesized that a direct ischemic impairment of myocardial relaxation is indeed responsible for the decrease in LV chamber distensibility during angina in humans but that its demonstration in isolated heart muscle requires careful attention to specific elements of the physiology of the anginal state. To test this hypothesis, we developed an isolated rabbit heart model that was perfused with fresh, whole rabbit blood. To simulate the physiology of angina, brief periods of low-flow ischemia were imposed, and myocardial energy demand was increased by superimposing pacing tachycardia. To ensure that our measurements reflected LV myocardial relaxation per se, the pericardium was removed, and the right ventricle was drained throughout the experiment. Because we imposed global low-flow ischemia, any effect of segmental dyssynchrony was eliminated. Our results demonstrated a substantial impairment of myocardial relaxation when the anginal state was simulated in this manner.

Materials and Methods

Experimental Preparation

A global angina physiology model that uses an isolated, blood-perfused rabbit heart was developed in our laboratory. Male, albino New Zealand rabbits (1–2 kg) were heparinized and anesthetized with sodium pentobarbital (50 mg/kg), and the thorax was opened. The pericardium was cut, and the heart was isolated. A perfusion cannula was inserted into the ascending aorta and positioned immediately above the aortic valve, and the coronary arteries were perfused via the aortic root with fresh, whole heparinized rabbit blood. A large heparinized rabbit served as the blood donor and contributed 100–125 ml of fresh whole blood. The interval between isolation of the heart and initiation of coronary perfusion was less than 10 seconds. The heart was placed in a water-jacketed constant temperature chamber. The perfusion system consisted of a "venous" reservoir, a variable-flow pump, an oxygenator, a water-jacketed "arterial" reservoir, and a filter. In this system, the arterial reservoir was pressurized, and coronary perfusion pressure (CPP) was controlled by a valve that adjusted the pressure of the reservoir; coronary blood flow (CBF) was allowed to vary and depended on coronary vasomotor autoregulation (Figure 1).

After being pumped from the venous reservoir, the blood passed through an oxygenator into the pressurized reservoir and then through a filter of 40-μm pore size before entering the aortic cannula. The oxygenator was fabricated by coiling approximately 7.5 m of silastic tubing (0.58 mm i.d. and 0.77 mm o.d., Dow-Corning Corporation Medical Products, No. 602-235) as has been reported previously from this laboratory. The silastic tubing was placed inside a large beaker that was covered and equilibrated with a gas mixture of 20% O$_2$, 3% CO$_2$, with N$_2$, as the balance to achieve an arterial PO$_2$ of 90–100 mm Hg. Hematocrit of the blood ranged from 29 to 33%. Glucose was added to the perfusing blood at a rate of 100 mg/dl/hr to maintain the glucose content in a range of 80–100 mg/dl throughout each experiment.

After initiation of coronary perfusion, a cannula was inserted into the pulmonary artery stump to completely collect and drain coronary venous effluent to a venous reservoir below the level of the heart. In this preparation, the right ventricle was always flaccid and empty. The vena cavae were ligated. A drainage cannula was placed in the apex of the left ventricle to decompress that chamber of any Thebesian drainage. A thermistor (Yellow Springs Instruments) and a pacing electrode were inserted into the right ventricle via the right atrium. Myocardial temperature was maintained at 37° C. A collapsed latex balloon was placed in the left ventricle via the left atrium. The balloon was large in the apex of the left ventricle, above the aortic valve.
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enough so that no measurable pressure was generated by the balloon itself over the range of LV volumes used in this experiment.

CPP was measured from a side arm of the perfusion cannula connected to a pressure transducer (Statham P23Db). LV pressure was measured with a 3F micro-manometer catheter (Millar Instruments) that was connected to the intraventricular balloon or to a Statham P23Db transducer with a short length of stiff fluid-filled polyethylene tubing attached. The damping characteristics and natural resonant frequency response of this system have been described from this laboratory and satisfy the range shown by Falsetti et al to be required for accurate measurement of ventricular pressure and its first derivative. To assess LV chamber distensibility, LV balloon volume was kept constant so that an increase in left ventricular end-diastolic pressure (LVEDP) signified a decrease in diastolic chamber distensibility. A similar approach has been used previously in isovolumic heart models. The time constant of LV relaxation (T) was estimated by the linear regression of -dP/dt vs. P. The coronary flow rate was measured by timed samples of coronary venous effluent collected from the pulmonary artery cannula. We directly measured arterial and venous oxygen content (Lex-O2-Con, Lexington Instruments Corp.) and calculated the oxygen consumption from the arteriovenous oxygen content difference and the CBF. Arterial and coronary venous lactate content was measured by the specific enzymatic method of Apstein et al. All perfusate samples were immediately mixed with iced trichlor-acetic acid solution (final concentration of 5% TCA) and kept under refrigeration until chemical analysis.

Stability of the Isolated, Blood Perfused Rabbit Heart Preparation

In a series of 5 hearts perfused at a CBP of 80 mm Hg, contractile performance after 30 minutes of an initial “warm up” period resulted in an LV developed pressure of 92 ± 10 mm Hg at LVEDP = 10 mm Hg. With LVEDP constant at 10 mm Hg, developed pressure was constant at 30 minutes and declined by only 6% at 60 minutes. Diastolic function, assessed from the LV pressure-volume curves as the end-diastolic volume at an LVEDP = 10 mm Hg, was stable throughout the perfusion period, as was arterial P0, and hematocrit and blood lactate levels. The glucose level of the recirculated blood declined by 8% over 150 minutes. This preparation is stable during the length of time required for our experimental protocol described below.

Experimental Protocol

Preischemic measurements. LV volume was initially adjusted to achieve an LVEDP of 15 mm Hg under control conditions of a CPP of 100 mm Hg. A physiologic-paced heart rate of 4 Hz was used as the baseline rate because this frequency slightly exceeds the spontaneous rate of the normothermic isolated rabbit heart and allows for pacemaker capture without interference from endogenous pacemaker activity. We have also observed the heart rate of resting unanesthetized rabbits to be 3.5–4.5 Hz in our laboratory. The balloon volume was then kept constant for the remainder of the experiment. These steady-state conditions were maintained for 30 minutes. We then determined the paced heart rate in each heart for which the LV rate–systolic pressure product was maximal because we wished to select a pacing-tachycardia heart rate that would attempt to maximize myocardial energy demand. To select the pacing-tachycardia heart rate, the rate–systolic pressure product in each heart was measured in response to 1 minute of pacing at 5, 6, 7, and 8 Hz. The paced heart rate was then returned to the baseline paced rate of 4 Hz.

Recordings of LV pressure and CBF and measurements of coronary arterial and venous oxygen and lactate content were then made under control conditions of a CPP of 100 mm Hg and heart rate of 4 Hz. Because tachycardia itself may be associated with incomplete relaxation between beats, LVEDP was measured during 5 seconds immediately after discontinuation of pacing, a maneuver that resulted in bradycardia with a prolonged diastole. The pacer was then returned to the control heart rate of 4 Hz.

Global low-flow ischemia. Next, CPP was reduced to 20 mm Hg for a total of 6 minutes to induce global low-flow ischemia. A CPP of 20 mm Hg was used because it is comparable to the perfusion pressure distal to severe coronary stenoses in patients with angina. Hemodynamic and metabolic parameters as described above were measured at the control heart rate of 4 Hz after 1 minute of global ischemia. During the next 5 minutes of global ischemia, the effects of two different heart rates were studied in two different groups: pacing tachycardia (6.4 ± 0.2 Hz, n = 7) was compared with continuation of the paced heart rate of 4 Hz (n = 7).

Results

Hemodynamic and metabolic data from baseline, low-flow ischemia, and recovery conditions are shown in Tables 1 and 2. Note that during the last 5 minutes of ischemia, the effects of two different heart rates were studied: pacing tachycardia (6.4 ± 0.2 Hz) versus continuation of the baseline heart rate of 4 Hz. During
Table 1. Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ischemia</th>
<th>Recovery 10 min</th>
<th>Recovery 20 min</th>
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</thead>
<tbody>
<tr>
<td>LVEDP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>14 ± 1</td>
<td>25 ± 4</td>
<td>17 ± 3</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Group B</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>101 ± 2</td>
<td>41 ± 4</td>
<td>82 ± 7</td>
<td>83 ± 5</td>
</tr>
<tr>
<td>Group B</td>
<td>94 ± 3</td>
<td>48 ± 2</td>
<td>82 ± 4</td>
<td>80 ± 4</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dev P, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>86 ± 3</td>
<td>13 ± 3</td>
<td>67 ± 7</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>Group B</td>
<td>80 ± 3</td>
<td>33 ± 3</td>
<td>67 ± 3</td>
<td>66 ± 4</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVP x HR, mm Hg x Hz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>407 ± 11</td>
<td>261 ± 26</td>
<td>329 ± 27</td>
<td>325 ± 20</td>
</tr>
<tr>
<td>Group B</td>
<td>377 ± 14</td>
<td>193 ± 9</td>
<td>326 ± 20</td>
<td>319 ± 16</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T, msec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>47 ± 3</td>
<td>140 ± 31</td>
<td>54 ± 6</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>Group B</td>
<td>42 ± 3</td>
<td>114 ± 19</td>
<td>48 ± 5</td>
<td>50 ± 9</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
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Baseline, coronary perfusion pressure of 100 mm Hg and paced heart rate of 4 Hz in both groups; Ischemia, reduction of coronary perfusion pressure to 20 mm Hg; Recovery, return of coronary perfusion pressure to 100 mm Hg and paced heart rate of 4 Hz in both groups; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; Dev P, left ventricular systolic developed pressure; LVP x HR, the product of left ventricular systolic pressure and heart rate; T, the time constant of left ventricular pressure decay calculated by the derivative method. Group A, superimposition of pacing tachycardia during low-flow ischemia (6.4 ± 0.2 Hz, n = 7); Group B, continuation of paced heart rate of 4 Hz during low-flow ischemia (n = 7).

Differences between groups were estimated by unpaired Student's t tests.

As shown in Figure 4, in the pacing-tachycardia group, LVEDP (assessed during long diastoles with transient cessation of pacing) rose from a baseline value of 14 ± 1 to 25 ± 4 mm Hg (p<0.01) after the total 6-minute period of low-flow ischemia in comparison with the 4-Hz group (13 ± 1 mm Hg to 14 ± 1 mm Hg). This rise in LVEDP in the pacing-tachycardia group was reversible and returned to baseline during the recovery period in all experiments. Thus, global low-flow ischemia caused a decrease in LV diastolic distensibility only with the superimposition of elevated energy demand (pacing-tachycardia group). The time constant, T, describing the rate of LV relaxation, became significantly more prolonged in response to 6 minutes of low-flow ischemia in the pacing-tachycardia group relative to the 4-Hz group, which had a lower pressure-rate product during global ischemia. However, it should be emphasized that the elevated LVEDP in the pacing-tachycardia group reached its nadir and then remained constant during long diastoles with transient cessation of pacing in each experiment; this indicated that both the extent and rate of isovolumic relaxation were impaired during low-flow ischemia in this group with the superimposition of elevated energy demand, relative to the group with lesser energy demand.

CBF was comparable in both groups at baseline and fell to a similar extent after 1 minute of global low-flow ischemia (Figure 5). No further change in CBF occurred during the superimposition of two differing heart rates during continued low-flow ischemia at a constant CPP of 20 mm Hg. Myocardial oxygen demand during continued low-flow ischemia at a constant CPP of 20 mm Hg. Myocardial oxygen

Table 2. Coronary Flow and Metabolic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ischemia 6 min</th>
<th>Recovery 10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVO₂ ml/min/100 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>10.0 ± 1.0</td>
<td>3.9 ± 0.9</td>
<td>7.9 ± 0.9</td>
</tr>
<tr>
<td>Group B</td>
<td>9.3 ± 0.6</td>
<td>3.3 ± 0.5</td>
<td>9.3 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CF ml/min/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>1.7 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>Group B</td>
<td>2.1 ± 0.3</td>
<td>0.5 ± 0.1</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A – V lactate, mM/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>0.31 ± 0.25</td>
<td>–1.79 ± 0.43</td>
<td>0.64 ± 0.48</td>
</tr>
<tr>
<td>Group B</td>
<td>0.01 ± 0.22</td>
<td>–1.41 ± 0.32</td>
<td>0.15 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
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</table>

MVO₂, myocardial oxygen consumption per 100 grams left ventricular wet weight; CF, coronary flow per gram left ventricular wet weight; A – V lactate, coronary arterial minus venous lactate concentration difference. Other abbreviations as in Table 1.
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FIGURE 2. Effects of two different levels of energy demand superimposed during global low-flow ischemia. A typical experiment from each group is shown. Global low-flow ischemia was produced for a total of 6 minutes by reduction of CPP from 100 to 20 mm Hg. To assess influence of two different levels of energy demand, two different heart rates were superimposed during the last 5 minutes of low-flow ischemia: pacing tachycardia of 6.4 ± 0.2 Hz (top panel, ●) versus continuation of the baseline paced heart rate of 4 Hz (bottom middle panel, ○). For each group, LVP under baseline conditions of CPP 100 mm Hg and heart rate of 4 Hz is shown in far-left column, in response to 1 minute of ischemia in left-middle column, in response to 6 minutes of ischemia in right-middle column, and following 20 minutes of recovery at CPP 100 mm Hg and heart rate of 4 Hz in far-right column. Under each condition, LVEDP was assessed during transient cessation of pacing to ensure completeness of diastolic relaxation. In response to 1 minute of low-flow ischemia, a slight fall in LVEDP was seen in each group, consistent with a reduction in coronary turgor. In response to 6 minutes of ischemia with the superimposition of pacing tachycardia (top panel), there was a marked increase in LVEDP, indicating decreased LV diastolic distensibility. In example shown, LVEDP increased from 8 to 17 mm Hg. Note that elevated LV diastolic pressure reached its nadir and remained constant during cessation of pacing and long diastoles, suggesting an impairment of both the rate and extent of LV relaxation. Decrease in LV diastolic distensibility did not occur in the group with lower energy demand (4-Hz group, bottom panel). This decrease in LV diastolic distensibility noted in the pacing-tachycardia group was reversible in the recovery period (far-right column).

consumption also fell to a similar extent following 1 minute of global ischemia. No further change in myocardial oxygen consumption occurred during continued low-flow ischemia, and it did not differ between the two groups. In both groups, the reduction in CPP from 100 to 20 mm Hg was accompanied by a shift from lactate consumption to comparable lactate production measured after 1 minute of low-flow ischemia (Figure 5). Lactate production measured after an additional 5 minutes of ischemia was also comparable in the pacing-tachycardia and 4-Hz groups.

To examine the influence of pacing tachycardia per se on LV diastolic function, the effect of a 5-minute period of pacing tachycardia (6.5 Hz) was studied in a separate group of rabbit hearts that were perfused under identical conditions at a CPP of 100 mm Hg. In comparison with baseline, there was no change in LVEDP in response to pacing tachycardia alone (n = 4, 15.8 ± 0.9 mm Hg versus 15.3 ± 0.9 mm Hg, NS).

Discussion

The experimental, isolated, blood-perfused heart preparation was developed in our laboratory for the purpose of duplicating the physiology of angina pectoris in a model of global low-flow demand ischemia. In this preparation, the reduction of CPP to 20 mm Hg resulted in the expected decline in systolic performance with no decrease in LV diastolic chamber distensibility as assessed by LV diastolic pressure with constant LV balloon volume. However, the imposition of brief (5 minutes) pacing tachycardia at a CPP of 20 mm Hg resulted in a substantial but completely reversible increase in postpacing LVEDP, which is indicative of a decrease in LV diastolic chamber distensibility. The hemodynamic changes observed are similar to those observed in patients with coronary stenoses who develop angina pectoris in response to exercise or pacing tachycardia and in whom an upward shift in the LV diastolic pressure-volume relation
In the group with pacing tachycardia superimposed during the demand is shown at baseline, at 1 and 6 minutes of global group. Levels of energy demand at baseline and in response to significantly higher than in the 4-Hz group.

**FIGURE 3.** Myocardial energy demand estimated by the product of LV systolic pressure and heart rate. This index of energy demand is shown at baseline, at 1 and 6 minutes of global low-flow ischemia; open circles indicate the 4-Hz group. Closed circles indicate the group with superimposition of pacing tachycardia during ischemia; open circles indicate the 4-Hz group. Levels of energy demand at baseline and in response to 1 minute of low-flow ischemia were comparable in both groups. In the group with pacing tachycardia superimposed during the last 5 minutes of global ischemia, the pressure-rate product was significantly higher than in the 4-Hz group.

occurs promptly after the onset of angina and is reversible if ischemia is relieved. A similar upward shift in LV pressure-volume relations and in LV diastolic pressure–segment length relations has been observed in open-chest dogs with coronary stenoses in whom regional ischemia was induced by pacing tachycardia. The mechanisms responsible for the increase in LV diastolic pressure relative to volume during demand ischemia have been controversial and are clarified by our demonstration that this phenomenon occurs in the globally ischemic heart without pericardial restraint and with an empty right ventricle.

**Pericardial and Ventricular Interaction Effects**

LV diastolic pressure can be modified by changes in right ventricular loading, with or without the pericardium. and these factors have been suggested as a possible factor in the rise in LV diastolic pressure that occurs during angina. In our model, a postspacing-tachycardia increase in LV diastolic pressure relative to constant LV volume occurred in the absence of the pericardium and with the right ventricle empty, thus excluding any major influence of the pericardium or right ventricular distension. Thus, although several studies demonstrate an effect of right ventricular loading and pericardial influence on LV filling, the studies of Momomura et al and the results from our experiment indicate that demand ischemia can directly influence myocardial relaxation independent of any right ventricular or pericardial effect.

**Influence of Dysynchrony**

LV dyssynchrony of the strength and duration of contraction in adjacent ischemic and nonischemic regions has also been suggested as a major mechanism responsible for abnormal LV diastolic function during angina. Both an elastic recoil of passively stretched ischemic segments and delayed active shortening could cause a decrease in LV diastolic chamber distensibility. Furthermore, Brutsaert et al have argued that any regional and temporal nonuniform distribution of load and muscle inactivation can influence LV relaxation. In this experiment, the isovolumic hearts were studied under conditions of global ischemia, and they contracted isometrically in such a manner that the phenomenon of a hypercontractile region adjacent to an ischemic region with systolic bulging and diastolic recoil was not a confounding factor. The argument that dyssynchronous contractile behavior of ischemic and nonischemic regions plays a major role in the diastolic abnormalities of angina has been compelling. Until now, the experimental duplication of angina diastolic physiology (an ischemic rapid and reversible rise in LV diastolic pressure relative to volume) has been consistently demonstrated only in animal models with coronary stenoses or partial occlusions, i.e., regional ischemia with some preservation of coronary flow.

**FIGURE 4.** LV diastolic chamber distensibility at baseline, in response to 1 and 6 minutes of global low-flow ischemia, and during recovery. In this isovolumic ballon-in-LV model, LVEDP reflects LV diastolic chamber distensibility. In both groups, LVEDP was comparable at baseline. A slight fall in LVEDP occurred in each group in response to 1 minute of low-flow ischemia, consistent with decrease in coronary flow. Global low-flow ischemia caused an increase in LVEDP (indicating decreased chamber distensibility) only with the superimposition of elevated energy demand (pacing-tachycardia group). As shown here, there was a rapid recovery of LV diastolic function when baseline conditions were restored (CPP 100 mm Hg and heart rate 4 Hz), and LVEDP had completely returned to baseline at end of the 20-minute recovery period.
hypothesis versus low-flow ischemia with and without pacing tachycardia in isolated, buffer-perfused rabbit hearts with constant volume LV balloon. Although global hypoxia with maintained coronary flow consistently caused a prompt and reversible increase in LV diastolic pressure (which was markedly accelerated by pacing), pacing tachycardia caused a rise in postpacing LVEDP in only 2 of 14 global low-flow ischemia experiments. The lack of a rise in postspacing LVEDP during global hypoxia was attributed to reduced turgor of the coronary vascular bed, which has been shown to modify LV diastolic chamber stiffness.25,31

In this study, in contrast to the findings of Serizawa et al11 who used isolated, buffer-perfused rabbit hearts, perfusion of isolated rabbit hearts with whole blood consistently resulted in a decrease in LV diastolic chamber distensibility in response to pacing tachycardia during global low-flow ischemia. There are several factors that could account for these differences between the isolated, blood- and buffer-perfused models. The contribution of the vascular bed to myocardial wall thickness is lost when coronary flow ceases or is markedly diminished and when the pressurized hydraulic support of LV diastolic chamber stiffness decreases acutely. In our study, a slight fall in LVEDP occurred within the first minute of low-flow ischemia in all experiments, which is consistent with a reduced turgor effect. Vogel et al32 showed that global ischemia of both isolated, buffer- and blood-perfused rabbit hearts caused a substantial increase in LV diastolic chamber distensibility. However, this effect was less profound in blood-perfused hearts, suggesting that blood perfusion during global low-flow ischemia in blood-perfused hearts may provide more hydraulic support within the myocardial wall than during global ischemia in buffer-perfused hearts. Our study clearly shows that the isolated, blood-perfused rabbit heart more closely duplicates the diastolic pathophysiology of angina pectoris than does an otherwise comparable buffer-perfused model.

Influence of Energy Demand

Our study does support prior observations from this laboratory18,21 that primary low-flow ischemia alone in the absence of an increase in myocardial energy demand is insufficient to cause an acute decrease in LV diastolic chamber distensibility. The current study showed that no significant increase in LV diastolic pressure relative to volume occurred as CPP was reduced from 100 to 20 mm Hg during the continuation of a paced rate of 4 Hz. The imposition of the brief stress of pacing tachycardia, which transiently increased myocardial energy demand in the face of a reduced coronary perfusion, was necessary to produce a transient and reversible decrease in LV diastolic chamber distensibility similar to that which occurs during angina pectoris. These findings are entirely consistent with multiple observations from other laboratories that have also shown that low-flow ischemia, i.e., a primary reduction in coronary perfusion, causes no change or an acute increase in global or regional diastolic distensibility.2,12,20,21

Influence of Relaxation

Multiple abnormalities of the LV isovolumic relaxation period have been described in angina pectoris6,8,9 and in experimental models of demand ischemia or hypoxia.10,18 Paulus et al19 used an open-chest dog model with coronary stenoses and showed that the postspacing upward shift in LV diastolic pressure–segment length relations was potentiated by caffeine without a further slowing of the rate of isovolumic relaxation. These data were interpreted as being consistent with a dissociation between the rate and extent of LV relaxation during ischemia, and a similar dissociation has been observed during reversible hypoxic contracture by Greene and Weisfeldt.22 Momomura et al23 have recently shown an upward shift in end-diastolic LV pressure–segment length relations during demand ischemia that is unlikely to be accounted for by an impaired rate of relaxation alone. In our study, we demonstrated that global low-flow ischemia resulted in an impaired rate of relaxation (T). In addition, the elevation of LV diastolic pressure relative to volume in the pacing-tachycardia group was maintained during long diastoles during transient cessation of pacing. These observations lend support to the argument that the diastolic abnormalities during angina are related in part to a reduced extent of LV tension inactivation and persistent myosin–actin interaction throughout diastole. Thus, both the rate and extent of LV relaxation were reduced in this model of demand ischemia.
Relation of Ischemic Myocardial Metabolism to Left Ventricular Distensibility Changes

Lactate production was not significantly higher in the pacing-tachycardia group that showed a marked increase in LVEDP in response to ischemia when compared with the 4-Hz group in which there was no ischemia-induced rise in LVEDP. These data support the hypothesis that glycolytic flux was increased during low-flow ischemia at a low level of energy demand (4-Hz group) but did not increase further with a greater elevation of energy demand (pacing-tachycardia group). This suggests that glycolytic ATP production can protect against a decrease in diastolic distensibility during low-flow ischemia at low-energy demand but not when energy demand is elevated.

Alterations of myocellular calcium metabolism during demand ischemia may have contributed to the decrease in chamber distensibility. The imposition of an increased rate of stimulation during ischemic depression of the ATP-dependent sodium-potassium pump could result in the elevation of cytosolic sodium. This, in turn, might augment diastolic calcium levels via the sodium-calcium exchanger and promote persistent diastolic myosin-actin interaction. Also, the higher rate of stimulation during pacing tachycardia could have directly increased intracellular calcium content because of the increased frequency of depolarizations and accompanying increase in calcium slow channel flux. Thus, the combination of low-flow ischemia and pacing tachycardia may simultaneously increase cytosolic calcium but reduce ATP availability to energy-dependent pumps in the sarcoplasmic reticulum and sarcolemma that normally restore cytosolic calcium and sodium during diastole. The net result of a persistent increase in cytosolic calcium levels during diastole could account for the increase in diastolic tension observed under these conditions of simulated angina.

Limitations of the Model

Potential differences between the physiology demonstrated in our model and that of angina pectoris in humans should be addressed. First, the rise in LV diastolic pressure relative to volume during angina pectoris usually occurs in the presence of normal aortic pressure. In our study, the rise in postspacing-tachycardia LV diastolic pressure was observed at a CPP of 20 mm Hg. This value is, in fact, comparable to the values of CPP distal to coronary artery stenoses in patients with angina pectoris, estimated by the grade of stenosis and by the data of Gould and Lipscomb.

A substantive difference between this model and patients with clinical-effort angina is that basal coronary flow is usually adequate to meet myocardial oxygen requirements in this clinical setting. In this model, LV systolic function was extremely depressed at this level of CPP and global depression of coronary flow. This degree of global LV systolic dysfunction is not usually observed during angina in humans or in open-chest animal models with coronary stenoses. Although myocardial ischemia per se contributed to the decrease in systolic function in our model, the following additional factors should be pointed out. First, in our model, the heart was isolated and LV volume was kept constant. In the clinical situation and in open-chest animal models with coronary stenoses, LV volume during ischemia may increase when distensibility decreases in the ischemic regions. Thus, in these models, an increased preload on the nonischemic myocardium during demand ischemia may sustain systolic performance. Secondly, in our model, global ischemia was employed and included the right coronary and septal arteries. In open-chest animal models with coronary stenoses, perfusion of the right coronary and septal arteries was maintained normally; thus, myocardial regions that were normally perfused could contribute more to LV systolic pressure generation in these experiments than in our model of global ischemia. Thus, in patients or experimental models of coronary stenosis, the afterload imposed on the ischemic myocardium is greater than in our model. The effect of the greater afterload would be to increase energy demand of the ischemic segment. Our model may underestimate the energy demand imposed on the ischemic segment during regional demand ischemia. Finally, the observations in this model do not exclude the remote possibility that brief ischemia could induce a transient change in the mechanical properties of elastin or myocardial structural components that could alter diastolic distensibility.

In summary, our observations in an isolated, blood-perfused rabbit heart model with global low-flow demand ischemia and increased myocardial energy demand suggest that the rise in LV diastolic pressure relative to volume is related primarily to the effect of demand ischemia on myocardial relaxation per se and does not depend on the presence of regional dysynchronous contraction of ischemic and nonischemic segments nor on a right ventricular or pericardial influence. The fundamental biochemical mechanisms responsible for the decrease in LV diastolic distensibility and associated impairment of relaxation during demand ischemia are uncertain; several possibilities include the derangement of subcellular metabolism, including ATP deficiency, cytosolic calcium overload, or increased sensitivity of the contractile proteins to a given concentration of diastolic calcium. Further studies of the cardiac biochemical changes that accompany the diastolic physiology of angina are needed to clarify this issue.

References


Key Words • Diastole • myocardial relaxation • myocardial ischemia • ventricular distensibility • angina • diastolic compliance
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