Acute pulmonary edema during hypertensive crisis has been attributed to acute left ventricular systolic failure secondary to increased afterload. We tested the hypothesis that the increase in coronary artery perfusion pressure associated with systemic hypertension could also contribute to increased left ventricular filling pressures by acutely increasing coronary intravascular volume and decreasing left ventricular diastolic compliance. Isolated isovolumic (balloon in left ventricle) normal rabbit hearts (n=13) with pericardium removed and right ventricle vented were blood perfused at an initial coronary artery perfusion pressure of 100 mm Hg; left ventricular balloon volume was adjusted to produce an initial left ventricular end-diastolic pressure of 15±1 mm Hg; left ventricular systolic pressure was 102±3 mm Hg. When coronary perfusion pressure was increased to 130±1 mm Hg to simulate a hypertensive crisis, coronary flow increased from 2.0±0.2 to 3.0±0.2 ml/min/g left ventricle (p<0.001), left ventricular systolic pressure increased to 116±4 mm Hg, and isovolumic left ventricular end-diastolic pressure increased to 21±1 mm Hg (p<0.001), which indicated a decrease in left ventricular diastolic compliance. When coronary perfusion pressure was decreased to a physiological level of 70 mm Hg, coronary flow rate decreased to 1.4±0.1 ml/min/g left ventricle (p<0.001), left ventricular systolic pressure fell to 82±4 mm Hg, and left ventricular end-diastolic pressure fell to 14±1 mm Hg (p<0.001). The left ventricular diastolic pressure–volume curve was shifted upward and to the left at a coronary perfusion pressure of 130 mm Hg relative to the curve generated at a coronary perfusion pressure of 70 mm Hg, confirming that left ventricular diastolic compliance decreased when coronary perfusion pressure was elevated. Coronary hypertension also resulted in an increase in left ventricular wall thickness as assessed by two-dimensional echocardiogram. Mean endocardial-to-epicardial wall thickness was 5.1±0.6 mm at a coronary perfusion pressure of 130 mm Hg and 4.1±0.4 mm at a coronary perfusion pressure of 70 mm Hg (p<0.05). Neither peak negative rate of change of pressure (−dP/dt) nor the exponential time constant of ventricular relaxation changed when coronary perfusion pressure was decreased from 130 to 70 mm Hg, which suggests that early diastolic relaxation was unaffected over the range of coronary perfusion pressure studied. The correlation between coronary hypertension, decreased left ventricular diastolic compliance, and increased wall thickness in the normal isolated isovolumic blood-perfused rabbit heart suggests that coronary vascular turgor may be a significant factor altering diastolic compliance of the left ventricle during acute hypertension. (Hypertension 1989;13: 598–606)

Hypertensive crisis frequently results in congestive heart failure and may precipitate acute pulmonary edema. The acute rise in pulmonary capillary pressure that leads to pulmonary congestion is usually attributed to acute left ventricular systolic failure secondary to an acute increase in afterload, that is, afterload mismatch. However, the increase in coronary perfusion pressure and flow associated with an acute rise in aortic pressure may also directly affect left ventricular diastolic function.

Previous work from this2-5 and other6-7 laboratories has demonstrated a direct relation between left ventricular diastolic compliance and coronary artery perfusion pressure and flow. In this report we have adopted the terminology of Gaasch et al8 who use the term ventricular compliance to indicate changes in diastolic pressures at a common or fixed diastolic
volume or parallel shifts in the position of the diastolic pressure-volume curve. Thus, reduced ventricular compliance refers to an increase in left ventricular end-diastolic pressure at a fixed left ventricular volume or a parallel shift of the left ventricular diastolic pressure-volume curve upward and to the left. The term compliance is to be distinguished from the term chamber stiffness or chamber distensibility, which, by current usage, imply assessment of the slope of the diastolic pressure-volume curve.

During states of reduced coronary artery perfusion pressure and flow (ischemia), ventricular compliance initially increases in association with a decrease in left ventricular diastolic wall thickness. Conversely, during states of increased coronary flow induced by vasodilation, left ventricular compliance decreases to a small degree in concert with an increase in diastolic wall thickness.2,3,7-9 These findings support the concept initially proposed by Salisbury et al10 in 1960 that distensibility of the left ventricle is directly affected by coronary vascular turgor, that is, the degree to which the coronary vascular tree is distended with blood. Therefore, we hypothesized that an acute increase in both coronary artery perfusion pressure and flow associated with acute aortic hypertension would substantially decrease ventricular diastolic compliance and contribute directly to increasing left ventricular diastolic filling pressure. We tested this hypothesis in the isolated, isovolumic blood-perfused normal rabbit heart in which we could impose acute aortic and coronary hypertension in the absence of acute systolic failure.

Materials and Methods

Isolated Isovolumic Blood-Perfused Heart

Heparinized male albino New Zealand rabbits (1-2 kg) were anesthetized with sodium pentobarbital (50 mg/kg). The thorax was opened, the pericardium cut, and the heart isolated. A perfusion cannula was positioned in the aortic root directly above the aortic valve; the coronary arteries were perfused with fresh whole heparinized rabbit blood. A separate heparinized rabbit served as the blood donor, contributing 80-100 ml fresh whole blood to which 2 mg of gentamicin was added to prevent bacterial growth. The interval between isolation of the heart and initiation of coronary perfusion was less than 10 seconds. The perfusion system (Figure 1) consisted of a venous reservoir, a variable-flow pump, an oxygenator, a water-jacketed arterial reservoir, and a filter. The arterial reservoir was pressurized so that coronary perfusion pressure could be controlled by a valve, which adjusted the pressure inside the reservoir; coronary blood flow was allowed to vary according to coronary vasomotor autoregulation.

After being pumped from the venous reservoir, the blood passed through an oxygenator into the pressurized arterial reservoir and then through a filter (40 μm pore size) before entering the aortic cannula. The oxygenator was made by coiling approximately 7.5 m silastic tubing (0.58 mm i.d. by 0.77 mm o.d) as has been reported previously from this laboratory.2 The silastic tubing was placed inside a large beaker that was covered and equilibrated with a gas mixture of 20% O2, 3% CO2, and 77% N2 to maintain arterial pO2 at 90-110 mm Hg and pH 7.35-7.42. Hematocrit of the blood ranged from 29 to 33%. Glucose was monitored every 30 minutes with Chemstrip reagent strips (Boehringer Mannheim Diagnostics, Indianapolis, Indiana), and glucose was added as needed to maintain blood glucose levels within a range of 80-120 mg/dl throughout each experiment.

After initiation of coronary perfusion, the left atrium was cut, and a drainage cannula was placed in the apex of the left ventricle to decompress that chamber of any Thebesian drainage. A drainage cannula was positioned in the right ventricle via the pulmonary artery to collect all venous effluent, keep the right ventricle decompressed, and eliminate any influence of right ventricular volume or pressure on left ventricular compliance. The distal pulmonary artery and all vena cavae were ligated. A thermistor and pacing electrode were inserted into the right ventricle via the right atrium. All hearts were paced at 3.5 Hz, which consistently exceeded the
endogenous heart rate of each rabbit. Recording electrodes were fixed to the right atrium. A double-cannulated collapsed latex balloon was placed in the left ventricle. Both cannulas exited through the mitral valve orifice and were tied in place at the atrioventricular groove. One cannula was connected to a pressure transducer; the second cannula was connected to a calibrated syringe, which was used to adjust balloon volume. The balloon was larger than the left ventricular cavity and completely filled it so that no measurable pressure was generated by the balloon itself over the range of volumes used in these experiments.

The preparation was submerged in warmed saline inside a water-jacketed chamber, and temperature was maintained constant at 37° C. The stability of this preparation has been reported. 11

**Hemodynamic Measurements**

Coronary perfusion pressure was measured from a side arm of the aortic perfusion cannula, which was connected to a Statham (Gould-Statham, Oxnard, California) P23Db pressure transducer. Isovolumic left ventricular pressure was measured from a short length of stiff fluid-filled polyethylene tubing connecting the intraventricular balloon to a Statham P23Db transducer. The damping characteristics and natural resonant frequency response of this system have been reported previously3 and satisfy the range shown by Falsetti et al. 12 to be required for accurate measurement of ventricular pressure. The effect of coronary artery perfusion pressure on left ventricular compliance was assessed by measurement of changes in left ventricular diastolic pressure at a fixed left ventricular volume 5 as well as by measurement of changes in the position of the left ventricular diastolic pressure-volume curve. Pressure-volume curves were generated by progressive filling of the left ventricular balloon with 0.2-ml increments of saline and measurement of the corresponding left ventricular diastolic pressure, beginning with a completely collapsed (zero volume) balloon and increasing the balloon volume until end-diastolic pressure was 20–25 mm Hg. To avoid any contribution of hysteresis or stress relaxation to observed shifts in the pressure-volume relation, left ventricular diastolic pressure was always measured 7–10 seconds after each addition of volume to the balloon and only during filling (not emptying) of the balloon. We have previously documented the reproducibility of filling curves obtained in this manner. 4

Left ventricular relaxation was assessed by two methods: peak negative rate of change of pressure (−dP/dt) and the exponential time constant of left ventricular pressure decay, calculated by the derivative method (from the linear regression of −dP/dt vs. pressure). 13–14

Left ventricular isovolumic systolic pressure and peak positive rate of change of pressure (+dP/dt) were recorded at each coronary perfusion pressure. Maximum developed pressure was measured from the complete pressure-volume curve at each perfusion pressure.

Coronary flow rate was measured by timed samples of coronary venous effluent collected from the pulmonary artery cannula.

**Measurement of Left Ventricular Wall Thickness**

Two-dimensional echocardiographic imaging of the isolated, perfused heart was performed by aiming a 5.0 MHz medium-focus mechanical transducer, coated with ultrasound gel, through a membranous latex aperture in the surrounding water jacket. The transducer was manipulated until a clear, circular short-axis view of the left ventricle was obtained at a level just below the tips of the mitral leaflets, with the collapsed right ventricle positioned posteriorly. The transducer was then clamped into position for the duration of the experiment.

All studies were recorded on standard 1/2 in. videotape, and wall thickness was later measured from digitized images by means of video calipers on a dedicated microcomputer. Wall thickness determination was made at the time of the R wave peak by measurement of the left ventricular free wall at the anterior (12 o'clock) position from endocardial (trailing edge) to epicardial (leading edge) borders. Measurements were made by an observer who was blinded to the conditions of each experiment.

In a subset of experiments, change in epicardial length was also measured under isovolumic conditions. We have previously shown that changes in isovolumic epicardial length correlate with changes in wall thickness measured by epicardial and endocardial ultrasonic crystals. 2 A mercury-in-silastic epicardial length gauge, 13 10 mm unstressed length, was sutured to the epicardial surface of the left ventricular free wall in a horizontal orientation along the equatorial circumference of the heart midway between the base and apex. The gauges were mounted with a slight degree of initial stretch so that slack in the gauge would not compromise measurement of segment length. Strain gauge length was recorded simultaneously with the aortic and left ventricular pressure signals; data is reported as change in length, in millimeters.

**Experimental Protocol**

All hearts (n=18) underwent a 30-minute warm-up period at a coronary artery perfusion pressure of 100 mm Hg with left ventricular balloon volume adjusted to produce a left ventricular diastolic pressure of 15 mm Hg. Balloon volume at this diastolic pressure became the control balloon volume for each heart for the duration of the experiment. Initial measurements of coronary flow and left ventricular pressure were obtained.
### Table 1. Changes in Left Ventricular End-Diastolic Pressure and Wall Thickness During and After Reversal of Coronary Artery Hypertension

<table>
<thead>
<tr>
<th></th>
<th>CPP (mm Hg)</th>
<th>Coronary flow (ml/min/g left ventricle)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Echo h (mm)</th>
<th>Segment length change (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive followed by normotensive coronary artery perfusion pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>3.0±0.2</td>
<td>116±4</td>
<td>21±1</td>
<td>5.1±0.6</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>1.4±0.1</td>
<td>82±4</td>
<td>14±1</td>
<td>4.1±0.4</td>
<td>−0.32±0.10 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0025</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.005</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Normotensive followed by hypertensive coronary artery perfusion pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>1.1±0.3</td>
<td>71±9</td>
<td>11±1</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>3.9±0.9</td>
<td>100±7</td>
<td>21±1</td>
<td>+0.38±0.06 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.025</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPP, coronary artery perfusion pressure; LVSP, peak left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; Echo h, echocardiographic wall thickness. All p values are for paired t test.

### Acute Coronary Hypertension

Coronary perfusion pressure was increased (over 3–5 minutes) to 130 mm Hg or until coronary perfusion pressure began to exceed peak left ventricular systolic pressure. The level of imposed hypertension was limited to 140 mm Hg or less to avoid the possibility of excessive edema formation. When left ventricular pressure had stabilized (approximately 5 minutes), measurements of coronary flow rate, left ventricular isovolumic systolic and diastolic pressure, and epicardial segment length were obtained. A two-dimensional echocardiogram was recorded on videotape, and a left ventricular filling curve was generated.

### Reversal of Coronary Hypertension

After left ventricular balloon volume was returned to the control volume, coronary perfusion pressure was reduced to 70 mm Hg. When left ventricular pressure had stabilized (approximately 5 minutes), measurements of coronary flow rate, left ventricular isovolumic systolic and diastolic pressure, and segment length were obtained; a two-dimensional echocardiogram was recorded, and a left ventricular filling curve was generated. At the conclusion of the experiment, the heart was removed from the apparatus, the left ventricle was dissected free, and wet weight/dry weight ratio was determined.

### Reversed Sequence of Perfusion Pressure Changes

In a second series of hearts (n=5), after a period of baseline control perfusion at a coronary perfusion pressure of 100 mm Hg, the coronary perfusion pressure was first decreased to 70 mm Hg and then increased to 130 mm Hg. Coronary flow rate, left ventricular isovolumic systolic and diastolic pressure, segment length, two-dimensional echocardiographic wall thickness, and filling curves were measured at each level of coronary artery perfusion pressure. At the end of each experiment, the left ventricle was isolated for wet and dry weight determination.

### Assessment of Myocardial Edema

To assess the possible contribution of coronary hypertension-induced myocardial edema to observed changes in left ventricular compliance, we compared wet weight/dry weight ratios of hearts exposed to high coronary artery perfusion pressure with a series of hearts exposed only to normal levels of perfusion pressure. A separate series of similarly prepared isolated hearts (n=5) were perfused at a coronary perfusion pressure of 70 mm Hg for 45 minutes such that the total duration of perfusion was comparable with the total duration of the acute hypertension protocols. The wet weight/dry weight ratio in these hearts was compared with the wet weight/dry weight ratio of hearts subjected to both hypertension protocols described above, that is, hypertension followed by normalization of perfusion pressures and normal perfusion followed by hypertension.

### Statistical Analysis

Data are expressed as the mean±SEM. Comparisons of the means of parameters measured at different coronary artery perfusion pressures were by Student’s paired t test. Left ventricular diastolic pressure-volume curves were analyzed by linear regression of the equation:

\[
\text{LVEDP}=a(\text{LV vol})+b
\]

where LVEDP is the left ventricular end-diastolic pressure and \( \text{LV vol} \) is the left ventricular balloon volume. The means of the constants \( a \) and \( b \), representing slope and position, respectively, of the curves obtained at each level of coronary artery perfusion pressure were compared by Student’s paired t test.

### Results

At the end of the control warm-up period, during which the heart was perfused at a coronary artery perfusion pressure of 100 mm Hg, coronary flow rate was 2.0±0.2 ml/min/g left ventricular wet wt. The volume of the left ventricular balloon was adjusted to produce an end-diastolic pressure of...
The effects of coronary hypertension on left ventricular diastolic compliance are shown in Table 1 and Figure 2. The change in coronary blood flow, left ventricular isovolumic systolic and diastolic pressure, echocardiographic left ventricular wall thickness, and epicardial segment length after coronary artery perfusion pressure was decreased from hypertensive levels (130 mm Hg) to physiological levels (70 mm Hg). The increase in wall thickness (Figure 3). Mean echocardiographic wall thickness was 5.1±0.6 mm at a coronary artery perfusion pressure of 130 mm Hg compared with 4.1±0.4 mm at a coronary perfusion pressure of 70 mm Hg (p<0.05). Isovolumic epicardial thickness, and epicardial segment length after coronary artery perfusion pressure was 5.1±0.6 mm at a coronary perfusion pressure of 130 mm Hg, comparable changes in end-diastolic pressure and segment length were observed (Table 1).

When analyzed by fitting the pressure-volume curve data points at each coronary artery perfusion pressure to the linear regression equation LVEDP=a(LV vol)+b, there was no significant difference in the means of the slopes (a) of the curves; however, the means of the y intercepts (b) were significantly different at a coronary perfusion pressure of 130 mm Hg (−34.7±6) compared with a coronary artery perfusion pressure of 70 mm Hg (−47.1±6, p<0.001). Thus, the position of the diastolic pressure-volume curve obtained at a coronary artery perfusion pressure of 130 mm Hg was shifted significantly upward and to the left relative to the curve obtained at a physiological coronary artery perfusion pressure of 70 mm Hg, consistent with a decrease in left ventricular compliance at the higher coronary artery perfusion pressure. When the sequence of alterations in coronary artery perfusion pressure was reversed (70 mm Hg followed by 130 mm Hg), a similar shift in the position of the left ventricular diastolic pressure-volume curve was seen.

There were no significant changes in rate of early left ventricular relaxation at different coronary perfusion; neither peak −dP/dt nor the exponential time constant of left ventricular relaxation (from the linear regression of −dP/dt vs. pressure) were significantly different when measured at a coronary perfusion pressure of 130 mm Hg versus 70 mm Hg (Table 2).

Left ventricular systolic performance improved when coronary perfusion pressure was increased. Peak +dP/dt was significantly higher at a coronary perfusion pressure of 130 mm Hg than at 70 mm Hg (1,644±76 vs. 1,335±58 mm Hg/sec, p<0.001), and maximum developed pressure increased (93±15 vs. 80±12 mm Hg, p<0.05).

We considered the possibility that coronary hypertension might induce interstitial edema and that this might contribute to the observed changes in left ventricular compliance. We compared the wet weight/dry weight ratios of three groups of hearts (Table 3). Group 1 was exposed to the sequence of decreasing perfusion pressure (130–70 mm Hg); group 2 was exposed to the sequence of increasing perfusion pressure (70–130 mm Hg); group 3 was exposed to a similar total duration of perfusion (45 minutes) but at a stable perfusion pressure of 70 mm Hg. There were
no significant differences in wet weight/dry weight ratios among the three groups, which suggests that there was no significant increase in edema formation associated with the levels of coronary artery perfusion pressure used in these experiments.

**Discussion**

In the isolated isovolumic blood-perfused rabbit heart, an increase in mean aortic perfusion pressure comparable with that observed during acute hypertensive episodes (from 70 mm Hg to 130 mm Hg) was associated with a decrease in left ventricular compliance, that is, with a shift in the left ventricular diastolic pressure-volume relation upward and to the left such that left ventricular end-diastolic pressure was significantly increased for any level of diastolic volume. This reversible decrease in ventricular compliance induced by coronary hypertension occurred in association with a reversible increase in diastolic wall thickness, demonstrated both by echocardiography and by epicardial segment-length gauge.

Directionally similar changes in left ventricular compliance and wall thickness were observed when coronary perfusion pressure was varied between 70 and 100 mm Hg, but the measured changes in isovolumic left ventricular end-diastolic pressure, left ventricular wall thickness, and position of the left ventricular diastolic pressure-volume curve did not reach statistical significance.

Although not the focus of this study, we also observed changes that suggested a small improvement in systolic function in response to coronary artery hypertension. Isovolumic left ventricular systolic pressure, peak +dP/dt, and maximum developed pressure were significantly greater at a coronary artery perfusion pressure of 130 mm Hg than at 70 mm Hg. Two mechanisms may contribute to this observation: the Frank-Starling mechanism and the Anrep effect. Arnold and colleagues suggested that distension of coronary vessels during coronary hyperperfusion (the "garden-hose" effect) increased myocardial fiber length, thus enhancing mechanical function by the Frank-Starling mechanism. Many investigators have demonstrated a positive inotropic response to an increase in aortic pressure, an effect first described by Von Anrep (and by Knowlton and Starling) in 1912. The mechanism of the Anrep effect is unclear. Vatner and colleagues suggested that the effect is a consequence of hyperemia after transient subendocardial ischemia induced by the acute increase in aortic pressure. However, this effect is not entirely dependent on an increase in coronary flow since the phenomenon can be demonstrated, albeit to a more modest extent, in models in which aortic pressure is acutely increased while coronary flow is held constant and force-velocity analyses suggest that

**TABLE 2. Effect of Coronary Artery Perfusion Pressure on Left Ventricular Relaxation**

<table>
<thead>
<tr>
<th>CPP (mm Hg)</th>
<th>T (msec)</th>
<th>Peak -dP/dt (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>54±6</td>
<td>-1104±51</td>
</tr>
<tr>
<td>70</td>
<td>48±4</td>
<td>-1012±47</td>
</tr>
</tbody>
</table>

CPP, coronary artery perfusion pressure; T, time constant of left ventricular pressure decay calculated by the derivative method; NS, not significant.

**TABLE 3. Comparison of Wet Weight/Dry Weight Ratios in Three Groups of Hearts**

<table>
<thead>
<tr>
<th>Group</th>
<th>Coronary artery perfusion pressures</th>
<th>Wet/dry weight ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130 mm Hg-70 mm Hg</td>
<td>5.3±0.2 (n=5)</td>
</tr>
<tr>
<td>2</td>
<td>70 mm Hg-130 mm Hg</td>
<td>5.0±0.10 (n=13)</td>
</tr>
<tr>
<td>3</td>
<td>70 mm Hg</td>
<td>5.1±0.05 (n=5)</td>
</tr>
</tbody>
</table>

NS, not significant.
the increase in systolic performance represents a true net positive inotropic effect. This effect does not appear to be mediated by release of catecholamines as it has been observed after β-adrenergic blockade.

Most textbooks attribute the acute pulmonary congestion associated with hypertension crisis to systolic failure secondary to excessive afterload. However, this concept may not explain the sole mechanism of pulmonary congestion in acute hypertensive states. The decrease in left ventricular compliance associated with increased wall thickness at increased coronary artery perfusion pressures provides an alternative or additional mechanism of acute pulmonary congestion in acute hypertensive states.

Previous work has suggested that coronary artery perfusion pressure and flow can significantly modify left ventricular diastolic properties although none have specifically addressed hypertensive states. In 1960, Salisbury et al. reported that coronary artery perfusion pressure was inversely proportional to left ventricular diastolic distensibility in isovolumic contracting dog hearts. They speculated that a passive increase in coronary blood volume retained within the coronary arteries and veins (turgor) would change the resiliency of the coronary vascular tree and thus change the elastic properties of the heart. Additional studies have confirmed this hypothesis about the relations among coronary flow, myo-cardial blood volume, and wall thickness, and several have related these changes to alterations in left ventricular diastolic–volume relations.

During states of increased coronary artery blood flow induced either by vasodilators, postischemic hyperemia, or hyperemia induced by hypoxemia, ventricular compliance has been shown to decrease. However, in each of these studies, the coronary perfusion pressure either decreased or was held constant as part of the experimental protocol. Verrier and colleagues demonstrated a small shift in the left ventricular diastolic–dimension curve compatible with reduced compliance in intact dog hearts when coronary blood flow was increased by drug-induced vasodilation; however, coronary perfusion pressure declined in this study, and the authors speculated that the effect may have been much greater had coronary perfusion pressure not decreased.

The effects of increased coronary artery perfusion pressure on left ventricular diastolic properties have been investigated previously but with conflicting results. Olsen and colleagues reported a leftward shift in the left ventricular diastolic pressure–dimension curve in arrested dog hearts on right ventricular bypass when coronary artery pressure was increased from 40 to 120 mm Hg although they noted that the greatest changes occurred below the autoregulatory range (≤80 mm Hg). Alderman and Glantz showed in humans that the left ventricular pressure–volume curve shifted upward and to the left when aortic pressure was increased to hypertensive levels by angiotensin infusion. They speculated that external mechanical loading conditions (right-left ventricular interaction and pericardial restraint) and the viscoelastic properties of the cardiac muscle were the key factors altering the left ventricular diastolic pressure–volume relation. In contrast to these studies, Abel and Reis reported no change in isovolumic left ventricular end-diastolic pressure in an intact balloon-in-left ventricle canine model on right ventricular bypass either when coronary artery perfusion pressure was decreased to ischemic levels or increased to 150 mm Hg. With use of a similar model, Templeton and colleagues reported no change in either the position or slope of the left ventricular diastolic pressure-volume curve in isovolumic dog hearts when coronary perfusion pressure was increased. However, only a modest increase in coronary perfusion pressure from 60 to 95 mm Hg was imposed, and this is consistent with our observation that the decrease in compliance was significant only when coronary perfusion pressure was increased from 70 to 130 mm Hg and was not statistically significant over the range of 70–100 mm Hg.

In the present study, we have demonstrated a significant, rapidly reversible decrease in left ventricular compliance associated with coronary artery perfusion pressures in the hypertensive range. Left ventricular end-diastolic pressure was significantly increased at a fixed diastolic volume, and there was a parallel shift upward and to the left of the left diastolic pressure–volume curve. We did not observe any change in the slope of the diastolic pressure–volume curve so that calculated chamber stiffness, as defined by Gaasch et al., was unchanged over the range of perfusion pressures we studied. We have previously observed that both the position and the slope of the pressure–volume curve change when the heart is subjected to injury by hypoxia or protracted ischemia. However, alterations in pressure and flow induced by adenosine shifted only the position of the diastolic pressure–volume curve and had little if any effect on the slope. Parallel shifts in the position of the diastolic pressure–volume curve in the absence of changes in slope have been described by others during acute interventions in intact animals and have been primarily ascribed to external forces, such as pleural and pericardial pressure or right-left ventricular interaction, which can be discounted in our model. The reversible increase in wall thickness we observed suggests that the decrease in ventricular compliance resulted, at least in part, from an increase in coronary vascular turgor, that is, in decreased distensibility of the ventricular wall secondary to vascular engorge-ment. However, several other factors that might modify diastolic properties of the left ventricle in this model should be considered.
Myocardial Interstitial Edema Formation

Cross and colleagues demonstrated in the isolated blood-perfused dog heart that myocardial interstitial edema (≥4–5% heart weight) reduced left ventricular compliance. However, Salisbury et al did not find evidence of significant edema formation in blood-perfused hearts when the degree of hypertension was limited to less than 140 mm Hg. It is possible that the small gradient between maximum coronary artery perfusion pressure and peak left ventricular systolic pressure that developed in some hearts may have magnified the coronary vascular engorgement or permitted accumulation of interstitial edema at coronary perfusion pressures of less than 140 mm Hg. However, we did not find evidence of increased myocardial edema formation associated with hypertension. The wet weight/dry weight ratios of hearts perfused at a stable coronary artery perfusion pressure of 70 mm Hg was not significantly different from those hearts subjected to periods of coronary hypertension at 130 mm Hg, consistent with the findings of Salisbury et al. Furthermore, there was no correlation between the degree of leftward shift of the diastolic pressure–volume curve and presence or absence of a small gradient between hypertensive coronary artery perfusion pressure and peak left ventricular systolic pressure.

Effects of Increased Afterload

The velocity of early diastolic relaxation is reduced when wall stress, that is, afterload, is increased throughout the period of tension development in the isovolumic heart. Changes in wall stress can be estimated from changes in the components of the Laplace relation, stress = Pr/2h where P is intraventricular pressure, r is the midwall radius of the sphere, and h is wall thickness. During the coronary hypertension experiments, peak left ventricular systolic pressure increased only modestly; left ventricular balloon volume was held constant, so that endocardial radius was not changed, but wall thickness increased so that midwall and epicardial radius were increased. It is not clear whether increased wall thickness induced by coronary vascular engorgement diminishes wall stress and stress imposed on the myocytes, as it does in left ventricular hypertrophy, or increases it, due to increased diastolic fiber length. Furthermore, it has been suggested that an acute increase in coronary artery perfusion pressure may actually enhance the rate of early diastolic relaxation by imposition of an early distending pressure on the myocardium as the coronary vasculature fills under increased pressure. We compared the rate of early relaxation at coronary perfusion pressures of 70 mm Hg and at 130 mm Hg. No differences were observed in either the time constant of left ventricular pressure decay or in peak -dP/dt (Table 2). It is possible that in this experimental model the effects of the modest increase in afterload to decrease the rate of early diastolic relaxation were exactly counteracted by the effects of increasing coronary vascular diastolic distending pressure to enhance early diastolic relaxation.

In clinical hypertensive crisis, in which there is a greater increase in peak systolic pressure than occurs in our isolated heart model, the role of impaired relaxation secondary to increased afterload may be more significant. Furthermore, since hypertensive crisis usually occurs in patients with a history of sustained hypertension, a variable degree of left ventricular hypertrophy may have a key role in determining diastolic compliance during acute hypertensive states. Increased total coronary resistance per gram of left ventricle in the hypertrophied heart may minimize the effect of acute increases in coronary perfusion pressure, and hypertrophy would attenuate the increase in wall stress. However, inherent differences in myocardial relaxation in the hypertrophied heart may make it more susceptible to further worsening of chamber compliance during acute coronary hypertension. Hypertensive crisis in a hypertrophied heart may be more likely to cause subendocardial ischemia than in a nonhypertrophied heart because of borderzone subendocardial perfusion failure and limited subendocardial coronary vasodilator reserve. Thus, in hypertrophied hearts, hypertensive crisis may alter diastolic compliance by several mechanisms, including increased coronary perfusion pressure and subendocardial ischemia.

In summary, acute coronary vascular engorgement associated with hypertensive coronary artery perfusion pressures in normal isolated blood-perfused rabbit hearts leads to a significant decrease in left ventricular compliance, which is rapidly reversible when coronary artery perfusion pressure is lowered. This phenomenon may contribute to development of acute pulmonary edema in hypertensive crisis in that the acute increase in systemic arterial pressure may affect not only systolic performance by acute afterload mismatch but may also alter diastolic compliance directly as a result of coronary vascular engorgement. The mechanism of rapid improvement in pulmonary congestion commonly observed with vasodilator therapy may be related to decompression of coronary vascular engorgement and improved diastolic compliance as well as to left ventricular unloading and improved systolic function.

Acknowledgments

We thank Dr. James J. Ferguson III for his assistance with the analysis of left ventricular relaxation. We also thank Dr. Margaret Ferrell for her contributions to this research and Nancy Ahonen for her help in preparing the manuscript.

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Hypertension. 1989;13:598-606
doi: 10.1161/01.HYP.13.6.598

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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