Acute Alterations in Left Ventricular Diastolic Chamber Stiffness

Role of the "Erectile" Effect of Coronary Arterial Pressure and Flow in Normal and Damaged Hearts

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SUMMARY. To separate the effects of coronary flow, perfusion pressure, and oxygen delivery on left ventricular diastolic compliance and diastolic wall thickness, isolated buffer and blood-perfused rabbit hearts with left ventricular volume controlled by a fluid-filled intraventricular balloon were subjected to the following interventions: complete global ischemia, hypoxia at constant coronary flow, hypoxia at constant coronary perfusion pressure, adenosine infusion at constant coronary flow, and at constant coronary perfusion pressure. Coronary flow, coronary perfusion pressure, left ventricular compliance curves, and diastolic epicardial circumference were measured during the 3rd minute of each intervention. Circumference changes were directly related to wall thickness changes when the isovolumic balloon was in place. Global ischemia caused a decrease in isovolumic diastolic epicardial circumference, a decrease in diastolic ventricular wall thickness, and an increase in diastolic compliance. Hypoxia with flow held constant caused an increase in diastolic circumference and a decreased diastolic compliance. Hypoxia with constant coronary perfusion pressure caused an increase in coronary flow, a further increase in diastolic epicardial circumference, and a further decrease in diastolic compliance. Adenosine infusion caused an increase in coronary flow, an increase in diastolic circumference, and a decrease in diastolic compliance. Adenosine infusion with constant coronary flow caused a decrease in perfusion pressure but caused no significant change in diastolic circumferential or the diastolic pressure-volume curve. The erectile properties of the myocardium (effect of coronary artery pressure on diastolic stiffness) were greater at larger ventricular diastolic volumes and pressures and in the injured heart (after 90 minutes of ischemia). These studies demonstrate a substantial direct "erectile" or "hydraulic" effect of the coronary vasculature on left ventricular diastolic properties; such an effect can influence diastolic ventricular filling and overall cardiovascular function and should be considered in interpreting changes in ventricular diastolic pressures in both experimental and clinical situations. (Circ Res 51: 465-478, 1982)

THE diastolic properties of the left ventricle are important determinants of cardiac function; their alteration in various forms of heart disease accounts for many of the clinical manifestations of congestive heart failure (Levine, 1972; Grossman and McLaurin, 1976). A number of complex variables have been reported to influence the diastolic behavior of the ventricle (Grossman and McLaurin, 1976); a direct effect of coronary artery pressure on diastolic compliance, i.e., an "erectile" or "hydraulic" effect of the coronary tree, has been previously suggested, but not completely defined (Salisbury et al., 1960; Sarnoff et al., 1960; Ahn et al., 1977; Serizawa et al., 1981), and its existence and significance is controversial (Grossman and McLaurin, 1976; Glantz and Parmley, 1978). Recently, nitroprusside infusion, given to decrease afterload and mean aortic pressure, has been demonstrated to shift the left ventricular diastolic pressure-volume relationship to the right, suggesting increased ventricular compliance. The change in pressure and volume in the intramural coronary arteries was suggested as one possible mechanism for this effect (Brodie et al., 1977).

Ventricular wall thickness is a major determinant of diastolic chamber compliance. Diastolic compliance and wall thickness have been shown to be linearly related under circumstances where wall thickness had increased on a chronic basis (usually as a result of a ventricular pressure overload) (Grossman et al., 1974; Grossman and McLaurin, 1976). Recently, postischemic hyperemia has been shown to induce acute changes in ventricular wall thickness (Gaasch and Bernard, 1977), and this mechanism of myocardial vascular engorgement therefore has the potential to decrease diastolic compliance. Increases in ventricular wall thickness during systole have been utilized as an index of contractile function, and the decrease in thickness which has been observed after coronary artery occlusion has been attributed to loss of regional contractility and passive stretching of the ischemic...
segment by the surrounding nonischemic myocardi-
mum (Heikkila et al., 1972; Ross and Franklin, 1976;
Corya et al., 1977); the effect of a coronary arterial
occlusion on diastolic wall thickness and diastolic
compliance as a result of a collapse of the intramy-
cardial vascular compartment has not received much
attention.

In the current study, we have demonstrated a direct
relationship between flow and pressure in the coro-
nary arterial tree and left ventricular diastolic chamber
stiffness and diastolic wall thickness in isolated rabbit
hearts. Acute changes in aortic and coronary arterial
pressure had an immediate and direct effect on left
ventricular diastolic filling properties and wall thick-
ness. These events can influence overall cardiovas-
cular function and should be considered in the inter-
pretation of ventricular diastolic pressure and wall
thickness measurements.

Methods

Surgical and Perfusion Technique

An isolated rabbit heart preparation was used for both
buffer and blood-perfusion studies. Male albino New
Zealand rabbits (1–2 kg) were decapitated and the thorax
opened. The pericardium was cut and the heart was cooled
with chilled saline (4°C). A drain was placed in the apex
of the left ventricle to decompress that chamber. A perfusion
cannula was inserted in the aorta at the level of the right
innominate artery and positioned immediately above the
aortic valve. Coronary arteries were perfused via the aortic
root with either Krebs-Henseleit buffer or red blood cell
 suspensions. The pulmonary artery was cut to allow free
ejection from the right ventricle. The remaining attachments
of the heart to the thorax were cut and the heart (without
the pericardium) was mounted on the perfusion apparatus.
The cut vena cavae and pulmonary artery were left open to
drain the right atrium and ventricle. In addition, a drainage
cannula was inserted into the right ventricle to ensure that
fluid would not accumulate in that chamber so that mea-
urements of left ventricular stiffness and dimensions would
not be influenced by right ventricular pressure or disten-
sion.

The apparatus used for Krebs-Henseleit buffer perfu-
sions was designed with two constant pressure reservoirs
and two reservoirs connected to a constant flow peristaltic
pump (Harvard, model #500-1200). Thus the hearts could
be switched from oxygenated to anoxic perfusate under
conditions of constant coronary flow or constant perfusion
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Measurement of Left Ventricular Wall Thickness, Circumference, and Pressures

A mercury-in-Silastic segment length gauge (Parrish et al., 1964), 10 mm unstressed length (Parks Electronics), was sutured to the epicardial surface of the left ventricular free wall in a horizontal orientation along the equatorial circumference of each heart about midway between base and apex. In certain experiments, a second length gauge was sutured in a vertical orientation perpendicular to the horizontal gauge. Each gauge was anchored by two superficial sutures through the underlying subepicardial myocardium; care was taken to avoid suturing coronary vessels. It is possible that the segment length gauge may have compressed epicardial or subepicardial coronary vessels, leading to local ischemia. Any such effect, however, is likely to be very mild, since we did not observe a decrease in left ventricular systolic pressure development when the gauge was attached. In contrast, accidental or intentional ligation of a coronary artery causes an abrupt and obvious decrease in developed pressure. The gauges were mounted with a slight degree of initial stretch so that slack in the gauge would not compromise measurements of segment length. In some experiments, changes in the absolute gauge length are reported in millimeters. In other experiments, external equatorial circumference was calculated from the gauge measurements in the following manner: left ventricular circumference at the level of the horizontal gauge was measured at the end of the experiment with the right ventricle removed, with the balloon in place, and with aortic pressure and left ventricular pressure equal to zero. The circumference was measured by snugly encircling the left ventricle with a suture, at the level of the length gauge, and measuring its length. Repeat measurements were reproducible within ±1 mm. Left ventricular circumference during the experimental manipulation was calculated from the segment length gauge reading by multiplying the gauge length measurements by the ratio of total circumference/gauge length determined at the end of the experiment.

In most of these experiments, a fluid-filled latex balloon was placed in the left ventricular chamber through the left atrial appendage and mitral orifice. The intraventricular balloon was connected to a pressure transducer (Statham P23Db) by a short length of stiff polyethylene tubing. Left ventricular diastolic compliance curves were generated by increasing the volume of saline in the balloon by 0.1-ml increments so that left ventricular end-diastolic pressure (LVEDP) varied between 0 and 35 mm Hg. To avoid variability due to stress relaxation and hysteresis, the same time interval (15 sec) was always used between volume increments, and diastolic pressures were always recorded during progressive filling of the balloon and not when fluid was being removed. The balloon was large enough that no measurable pressure was generated by the balloon itself over the volume ranges employed.

To ensure that observed effects of hypoxia and ischemia on left ventricular compliance measured with the intraventricular balloon were not due to some artifact of the balloon preparation, a series of experiments was performed in buffer-perfused hearts in which the left ventricular circumference and diastolic pressure were measured during direct filling of the left ventricle with saline through an apical cannula. A syringe infusion pump (Harvard model #190) was used and the ventricle was filled at a rate of 8 ml/min. Intraventricular pressures were measured from a side arm of the infusion cannula. At this infusion rate, there was no measurable pressure gradient between the open end of the infusion cannula and the side arm from which pressure was recorded. Before starting the filling curve, the left ventricle was gently compressed to empty it. The infusion was stopped when left ventricular diastolic pressure reached 30 mm Hg. Duplicate filling curves were superimposable, with diastolic pressure differing between two runs by no more than 1 mm Hg at any point during the filling curve. Because intraventricular volume was not measurable during the infusion (due to systolic ejection), LVEDP was plotted as a function of left ventricular epicardial circumference. The slope of this linear relationship was calculated by the method of least squares linear regression, and was used as a measure of the "effective stiffness" of the left ventricle.

In certain experiments (four hearts) thickness of the left ventricular free wall was measured with ultrasonic crystals. One crystal was wedged between the left ventricular anterior papillary muscle and the endocardial surface of the left ventricular free wall. Inflation of the intraventricular balloon to an end-diastolic pressure of 10-15 mm Hg held this crystal in place. An opposing crystal was sutured to the epicardium directly over the endocardial crystal. The crystals were oriented to transmit ultrasound in a transmural direction. The ultrasonic sonomicrometer system was manufactured by Parks Electronics. The crystals were calibrated by suspending them in saline and separating them by 1-mm increments; results are reported to the nearest 0.5 mm. When the separation between the crystals was less than 2.0 mm, a distorted signal was obtained and readings were not reliable. All of the wall thickness measurements recorded in these experiments were greater than 2.0 mm.

Experimental Protocols

Buffer-Perfused Hearts

Effects of Ischemia and Hypoxia on Ventricular Diastolic Compliance and Wall Thickness. In the first set of experiments, the effects of hypoxia and ischemia were studied in 10 intraventricular balloon preparations. Hearts were allowed to equilibrate for 30 minutes with coronary flow constant at 30 ml/min under control aerobic conditions (95% O2/5% CO2). A control diastolic compliance curve was generated, after which the following interventions were applied in each heart: global ischemia, during which coronary flow was completely shut off, hypoxia (95% N2/5% CO2) at constant flow of 30 ml/min, and hypoxia at constant coronary perfusion pressure. Constant perfusion pressure during hypoxia was adjusted for each heart to equal that measured during the constant flow aerobic control conditions. Compliance curves were measured during the 3rd minute after the onset of each intervention, after which the hearts were returned to control aerobic conditions for 20 minutes until the next intervention. During these 20 minute aerobic perfusion periods the hearts completely recovered from the brief periods of ischemia or hypoxia. The temporal order of interventions for different hearts was systematically varied. At 20 minutes after the final intervention, a second control compliance curve was repeated; final control values were not significantly different from the initial determinations and were averaged with the initial control measurements.

The ischemic and constant pressure hypoxia interventions were repeated in a separate set of eight hearts in which saline was infused directly into the left ventricular chamber (no intraventricular balloon). Filling curves were generated under three conditions: (1) coronary perfusion pressure = 100 mm Hg with oxygenated perfusate, (2) coronary perfusion pressure = 100 mm Hg with anaerobic perfusate, and (3) global ischemia, coronary perfusion pressure = 0.
The same sequence of measurements was followed in all hearts. First, the coronary perfusion pressure was adjusted to 100 mm Hg with oxygenated perfusate by regulating the variable coronary perfusion pump. Duplicate left ventricular filling curves were performed. The heart then was switched to the anaerobic perfusate, and the perfusion pump flow was adjusted to maintain a coronary perfusion pressure of 100 mm Hg. During the 3rd minute of hypoxia, duplicate filling curves were generated. The heart was allowed to recover for 20 minutes under control aerobic conditions. Coronary perfusion pressure was decreased to zero by turning off the perfusion pump and clamping the aortic perfusion line. During the 3rd minute of global ischemia, duplicate filling curves were generated.

Effects of Adenosine Infusion on Ventricular Diastolic Compliance and Diastolic Wall Thickness. To separate effects of coronary flow, perfusion pressure, and hypoxia on left ventricular diastolic wall thickness and compliance, two sets of experiments were performed using adenosine infusions. Six hearts, prepared with intraventricular balloons and epicardial segment length gauges, were perfused from the constant pressure reservoir at 80 mm Hg. After 30 minutes of equilibration, coronary flow was measured with balloon volume adjusted to produce a LVEDP of 10 mm Hg. A control compliance curve was generated. A solution of 3.3 mM adenosine dissolved in the perfusion buffer then was infused into a side arm of the perfusion cannula at a rate of 0.1 ml/min using a syringe pump. Preliminary experiments demonstrated that this produced maximal coronary vasodilation. During the 3rd minute of adenosine infusion, a compliance curve was generated and coronary flow was measured at a left ventricular end-diastolic pressure of 10 mm Hg. The adenosine infusion was halted. When coronary flow returned to its original value (which required 15 minutes or less), the control and adenosine runs were repeated. The duplicate runs were virtually superimposable.

In a separate group of six hearts, prepared with segment length gauges and intraventricular balloons, compliance curves and segment length changes during aerobic perfusion and constant flow hypoxia were compared to compliance and segment length during an adenosine infusion at constant coronary flow, to achieve the same degree of coronary vasodilation. During the 3rd minute of adenosine infusion, a compliance curve was generated and coronary flow was measured at a left ventricular end-diastolic pressure of 10 mm Hg. The adenosine infusion was halted. When coronary flow returned to its original value (which required 15 minutes or less), the control and adenosine runs were repeated. The duplicate runs were virtually superimposable.

Comparison of Circumferential Segment Length with Wall Thickness during Ischemia. In two sets of experiments, the epicardial segment length changes which occurred with global ischemia were further characterized. In four hearts with intraventricular balloons, epicardial segment length gauges were placed in both horizontal (equatorial) and vertical (base-apex) orientations. Absolute and percentage changes in horizontal and vertical segment length were compared during stepwise reductions of coronary flow. Coronary perfusion pressure was set at 90 mm Hg by adjusting the flow of the perfusion pump; left ventricular balloon volume was adjusted to produce a LVEDP of approximately 12 mm Hg. Coronary flow was decreased by adjusting the perfusion pump so that perfusion pressure decreased by 10 mm Hg increments. Hearts were held at each flow level for 30 seconds, and segment lengths and left ventricular end-diastolic pressures were recorded.

Four additional hearts were instrumented with horizontal epicardial segment length gauges and transmural ultrasonic crystals. Hearts were perfused from a constant pressure reservoir at a perfusion pressure of 80 mm Hg. Intraventricular volume was adjusted to produce a LVEDP of approximately 12 mm Hg. After an equilibration period, the aortic perfusion line was clamped to produce global ischemia. As aortic pressure decreased from 80 to 0 mm Hg, segment length and wall thickness were compared at 10 mm Hg increments of aortic pressure. Hearts were reperfused after 30 seconds of ischemia, and the runs were repeated after left ventricular systolic and diastolic pressures had returned to the initial values.

Effect of Diastolic Volume and Ischemic Injury on the Relationship between Coronary Perfusion Pressure and LVEDP ("Erectile" Effect). These studies were undertaken to define a potential interaction between the erectile effect and different pathological states. Specifically, in one series of experiments, diastolic volume was altered, as occurs in congestive failure, and the "erectile" effect was measured at different left ventricular diastolic volumes. In another series of experiments, the "erectile" effect was measured before and after ischemic injury.

Aortic perfusion pressure was set at 150 mm Hg by adjusting the rate of the perfusion pump, and balloon volume was adjusted to produce a LVEDP of 10 mm Hg. The perfusion pump was turned off and LVEDP was recorded as perfusion pressure fell from 150 to 5 mm Hg. The perfusion pump was turned back on, the hearts were allowed to recover, and the procedure was repeated with balloon volume increased to produce an initial LVEDP of 30 mm Hg. Perfusion then was resumed at a perfusion pressure of 150 mm Hg, and balloon volume was readjusted to produce a LVEDP of 10 mm Hg. The perfusion flow rate then was reduced to 0.1 ml/min for 90 minutes with balloon volume held constant. Pressure in the balloon rose gradually, during the 90 minutes, as the hearts developed ischemic contracture. At the end of the ischemic period, coronary perfusion pressure was again set at 150 mm Hg. After 15 minutes of reperfusion, the perfusion pressure was transiently reduced to produce a LVEDP vs. perfusion pressure; balloon volume was held constant at the value which produced a LVEDP of 10 mm Hg in the initial control period. Perfusion pressure was returned to 150 mm Hg. The transient ischemic run was repeated after 10 minutes with balloon volume adjusted to produce an initial LVEDP of 10 mm Hg.

Blood-Perfused Hearts

Several series of experiments were performed in blood-perfused hearts instrumented with an isovolumic left ventricular balloon and horizontal epicardial segment length gauge as described above. In one experimental series, the coronary perfusion pressure was adjusted to 100 mm Hg, the LVEDP was adjusted to either 12 or 30 mm Hg, and the perfusion pump was transiently turned off. The decrease in isovolumic ventricular diastolic pressure was plotted as a function of decreasing coronary perfusion pressure to define the magnitude of the "erectile" effect in blood-perfused hearts at different ventricular diastolic volumes.

In another series of experiments, left ventricular filling curves were performed as described above under the following conditions: (1) control conditions with coronary
perfusion pressure of 85 mm Hg and total coronary blood flow of 5.5 ml/min, (2) adenosine infusion (as described above) with coronary perfusion pressure held constant, and (3) adenosine infusion with coronary flow held constant.

Statistical Analysis
All averaged data are presented as a mean ± SEM. Values obtained during the various interventions are compared to the appropriate control values by the paired t-test.

Results
Buffer-Perfused Hearts
Effects of Ischemia and Hypoxia on Ventricular Compliance and Circumference

The effects of global ischemia and hypoxia in the intraventricular balloon buffer-perfused preparation are illustrated in Figure 1. The diastolic pressure-volume curve generated during global ischemia was shifted to the right relative to the control curve and the slope was less steep, indicating an increase in left ventricular diastolic compliance during acute, total global ischemia (i.e., no coronary flow or pressure). Hypoxia under conditions of constant coronary flow or constant perfusion pressure caused a shift to the left and an increase in the slope of the diastolic pressure-volume curve, indicating a decrease in diastolic compliance compared to the control state. When coronary flow was allowed to increase during constant perfusion pressure hypoxia, there was a significantly greater shift in the position and slope of the diastolic-pressure-volume curve compared to hypoxia at constant coronary flow.

To estimate the slope of the diastolic pressure-volume curves, ΔP/ΔV was calculated from the total change of balloon volume as left ventricular end-diastolic pressure (LVEDP) was increased from 5 to 30 mm Hg. The mean slope of the control curves was 53 ± 3 mm Hg/ml. During ischemia, slope decreased to 34 ± 3 mm Hg/ml (P < 0.001) and during constant flow hypoxia slope increased to 80 ± 7 mm Hg/ml (P < 0.02 vs constant coronary flow). When flow was allowed to increase during constant pressure hypoxia, the slope increased further to 91 ± 5 mm Hg/ml (P < 0.005). When flow was allowed to increase during constant pressure hypoxia, the slope increased further to 91 ± 5 mm Hg/ml (P < 0.02 vs constant flow hypoxia).

In these experiments, the changes in left ventricular diastolic compliance with ischemia and hypoxia were accompanied by changes in left ventricular epicardial diastolic circumference. As shown in Figure 2, epicardial diastolic circumference at any intraventricular balloon volume decreased markedly during global ischemia but increased during constant coronary flow hypoxia. Diastolic circumference increased further...
TABLE 1
Effects of Global Ischemia and Hypoxia

<table>
<thead>
<tr>
<th>Hypoxia (kQ)</th>
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<tr>
<td>CPP (mm Hg)</td>
<td>90 ± 4</td>
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<tr>
<td>CF (ml/min)</td>
<td>30</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10 ± 1</td>
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<tr>
<td>CIRC (mm)</td>
<td>62 ± 3</td>
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kQ = constant coronary flow; kP = constant coronary perfusion pressure; CPP = coronary perfusion pressure; CF = coronary flow; LVEDP = left ventricular end-diastolic pressure; CIRC = epicardial diastolic circumference.

* Indicates significant difference (P < 0.05) from control by paired t-test.
† Indicates significant difference (P < 0.05) between constant flow and constant pressure hypoxia.

when coronary flow was allowed to increase during constant perfusion pressure hypoxia. A summary of the changes in coronary perfusion pressure, coronary flow, LVEDP, and epicardial diastolic circumference under the four experimental conditions is presented in Table 1. These values were measured at the balloon volume which produced an LVEDP of 10 mm Hg under the control conditions (0.58 ± 0.07 ml).

The ischemia and constant perfusion pressure hypoxia interventions were repeated in eight hearts in which saline was infused directly into the left ventricular cavity, rather than into an intraventricular balloon. The slope of the line relating LVEDP to diastolic epicardial circumference ("effective stiffness") was used as an index of myocardial stiffness. The results were qualitatively similar to those obtained with the intraventricular balloon. Under control aerobic conditions, with coronary perfusion pressure set at 100 mm Hg, "effective stiffness" was 4.2 ± 0.6 mm Hg/mm circumference. Stiffness decreased to 2.8 ± 0.4 mm Hg/mm circumference during global ischemia (P < 0.01) and increased to 6.6 ± 1.2 mm Hg/mm circumference during constant perfusion pressure hypoxia (P < 0.025).

Effects of Adenosine Infusion on Ventricular Diastolic Compliance and Circumference

We hypothesized that the changes in epicardial diastolic circumference and diastolic compliance with ischemia and hypoxia could be caused during ischemia by a decrease of coronary intravascular volume resulting in decreased diastolic wall thickness, and decreased stiffness. Conversely, we reasoned that hypoxia causes vasodilation with coronary vascular engorgement, increased diastolic wall thickness, and increased diastolic chamber stiffness. To test this hypothesis, we examined the effect on ventricular diastolic compliance and epicardial diastolic segment length of an increase in coronary flow at constant perfusion pressure during coronary arterial adenosine infusion in a series of buffer-perfused hearts. Adenosine infusion at a constant perfusion pressure of 80 mm Hg caused an increase of coronary flow from 31 ± 4 to 47 ± 6 ml/min. The diastolic pressure-volume curve measured during adenosine infusion was shifted to the left as illustrated in Figure 3A. At the balloon volume which produced an LVEDP of 10 mm Hg in the control state, infusion of adenosine caused an increase of LVEDP to 14 ± 0.7 mm Hg (P < 0.005 by paired t-test). Adenosine infusion did not cause a significant change of slope of the diastolic pressure-
volume curve (ΔP/ΔV) which was 40 ± 2 mm Hg/ml in the control state and 37 ± 2 mm Hg/ml during the adenosine infusion. Epicardial diastolic segment length at any left ventricular balloon volume increased significantly during the adenosine infusion by about 4% as shown in Figure 3B.

To determine whether coronary vasodilation and possible vascular engorgement, without an increase in flow, could contribute to the increase in diastolic circumference and the shift of the diastolic pressure-volume curve observed during constant flow hypoxia, we compared the effects of hypoxia and adenosine infusion when coronary flow was held constant at 30 ml/min in buffer-perfused hearts. Coronary perfusion pressure during control aerobic perfusion was 84 ± 4 mm Hg. Hypoxic perfusion caused vasodilation with a decrease in coronary perfusion pressure to 58 ± 3 mm Hg (P < 0.005 compared to control by paired t-test). Adenosine infusion caused a similar decrease of perfusion pressure to 60 ± 3 mm Hg (P < 0.005 vs. control; P = NS vs. hypoxia). The effects of these interventions on the diastolic pressure-volume relationship are shown in Figure 4A. Hypoxia caused a significant shift of the diastolic pressure-volume curve to the left. The adenosine infusion, which caused an equal degree of vasodilation, had no significant effect on the diastolic pressure-volume relationship. The effects of constant coronary flow hypoxia and adenosine infusion on epicardial diastolic segment length are shown in Figure 4B. Epicardial diastolic segment length was increased at all balloon volumes during hypoxia but was unchanged during adenosine infusion when coronary flow was held constant.

Comparison of Diastolic Epicardial Segment Length and Wall Thickness in Ischemia

The dimension changes which occurred during global ischemia were examined further to determine whether the decrease in epicardial diastolic segment length which occurred during ischemia was due to a change in overall shape of the left ventricle or to thinning of the ventricular wall. Seven buffer-perfused hearts with epicardial segment length gauges in both horizontal and vertical orientations, and with balloon volume fixed to produce an LVEDP between 10 and 15 mm Hg, were studied. An example of such an experiment is shown in the top panel of Figure 5. Global ischemia caused horizontal diastolic segment length to decrease by 9.8% from 13.2 ± 0.6 to 11.9 ± 0.6 mm (P < 0.005), and vertical diastolic segment length to decrease by 8.3% from 12.1 ± 0.3 to 11.1 ± 0.3 mm (P < 0.001). The ratio of horizontal:vertical diastolic segment length was 1.09 ± 0.04 during control conditions and did not change significantly during global ischemia, during which the ratio was 1.07 ± 0.05. In four of these hearts, perfusion pressure was slowly decreased from 80 to 0 mm Hg by 10 mm Hg increments. As shown in the lower panel of Figure 5, the percent change in diastolic segment length for each decrement in perfusion pressure was similar in the horizontal and vertical directions. Thus, global ischemia caused equal relative decreases in both horizontal and vertical epicardial diastolic segment lengths with no apparent change in overall ventricular shape.

Since both vertical and horizontal diastolic circum-
Effect of Severe Ischemic Injury and LV Volume on the Relationship between Coronary Perfusion Pressure and LVEDP

To determine whether ischemic injury could alter the effect of coronary perfusion pressure on the diastolic pressure-volume relation, LVEDP was measured decreased by 7% from 11.0 ± 0.06 to 10.3 ± 0.2 mm, while left ventricular diastolic wall thickness decreased by 18% from 3.1 ± 0.2 to 2.5 ± 0.4 mm. 

References decreased and the intraventricular balloon maintained chamber volume constant, we concluded that left ventricular diastolic wall thickness must have decreased during global ischemia. To verify this conclusion, ultrasonic crystals were used to directly measure wall thickness during ischemia in four hearts. Diastolic segment length, diastolic wall thickness, and left ventricular diastolic pressure all decreased simultaneously with the fall in aortic perfusion pressure as illustrated in the top panel of Figure 6. A summary of transmural thickness plotted against epicardial diastolic segment length during the onset of global ischemia is presented in the lower panel of Figure 6. Diastolic segment length and diastolic wall thickness were linearly related as perfusion pressure fell from 80 to 0 mm Hg. Epicardial diastolic segment length decreased by 1% from 11.0 ± 0.06 to 10.3 ± 0.2 mm, while left ventricular diastolic wall thickness decreased by 18% from 3.1 ± 0.2 to 2.5 ± 0.4 mm.
ured as perfusion pressure was decreased from 150 to 5 mm Hg in four buffer-perfused hearts before and after a 90-minute period of global ischemia. The prolonged ischemia caused significant contracture in these hearts so that LVEDP increased to 26 ± 5 mm Hg (P < 0.001) at a balloon volume which initially produced a LVEDP of 10 mm Hg. The effect of altering coronary perfusion pressure before and after ischemia, with balloon volume constant, is shown in Figure 7A. The decrease in LVEDP as perfusion pressure was lowered was considerably greater in the postischemic hearts (P < 0.005).

It was not clear from this result whether the greater influence of perfusion pressure on LVEDP in the postischemic period was due to an effect of ischemic injury on the coronary perfusion pressure-LVEDP relationship, or was simply due to the fact that LVEDP was falling from a higher initial value. To distinguish between these possibilities, the effect of lowering perfusion pressure on LVEDP at larger LV volumes was greater at 30 mm Hg than at 10 mm Hg, indicating a greater influence of perfusion pressure on LVEDP in the postischemic period (P < 0.01 at initial LVEDP = 10; P < 0.05 at initial LVEDP = 30). The decreases of LVEDP and the slopes of the regression lines relating LVEDP and perfusion pressure from Figure 7 are summarized in Table 2.

A representative tracing showing the effect of a decrease in coronary perfusion on LVEDP before and after ischemic injury is shown in Figure 8. In this experiment, after ischemic injury, LVEDP decreased by 42 mm Hg, when coronary perfusion pressure was decreased from 150 to 10 mm Hg.

Blood-Perfused Hearts
The observations described above in buffer-perfused hearts clearly demonstrated a hydraulic or "erectile" effect of coronary flow and pressure on diastolic wall thickness and chamber stiffness. However, in order to maintain adequate oxygen delivery, all buffer-perfused heart preparations require a rate of coronary flow in excess of the in vivo value. To ascertain whether the observed hydraulic effects of the coronary vasculature were the result of the excessive coronary flow rates of the buffer-perfused preparation, a series of blood-perfused experiments was performed in which the control coronary blood flow rate was in the physiological range.

The results of a typical blood-perfusion experiment are shown in Figure 9. In the upper panel, the intra-left ventricular balloon volume was adjusted to produce an LVEDP of 10 mm Hg. Coronary blood flow, coronary perfusion pressure and left ventricular developed pressure were all in the physiological range. Transient global ischemia was induced by turning off the coronary perfusion pump; there was a simultaneous decrease in left ventricular diastolic pressure from 8 to 1 mm Hg, and a concomitant decrease in diastolic wall thickness as measured by the epicardial segment length gauge. The lower panel of Figure 9 shows the results from a similar experiment in which the control LVEDP was set at 27 mm Hg; LVEDP...
TABLE 2
Decrease in LVEDP with Fall in Coronary Perfusion Pressure

<table>
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<tr>
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<th>C10</th>
<th>C30</th>
<th>PI C</th>
<th>PI 10</th>
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<td>Δ LVEDP</td>
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<td>13.2 ± 1.6*</td>
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<td>Slope</td>
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<td>0.074 ± 0.004*</td>
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<td>0.044 ± 0.004*</td>
<td>0.106 ± 0.004†</td>
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<td>0.997</td>
<td>0.988</td>
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</tbody>
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C10 = control period; balloon volume set to produce LVEDP = 10 at Ao P = 150; C30 = control period; balloon volume set to produce LVEDP = 30 at Ao P = 150; PI C = postischemic; balloon volume = that used in C10; PI 10 = postischemic; balloon volume set to produce LVEDP = 10 at Ao P = 150; PI 30 = postischemic; balloon volume set to produce LVEDP = 30 at Ao P = 150; Δ LVEDP = decrease in LVEDP as coronary perfusion pressure fell from 150 to 5 mm Hg; slope = slope of regression lines illustrated in Figure 7; r = correlation coefficient of regression lines in Figure 7.

* Indicates P < 0.05 compared to C10 by paired t-test.
† Indicates P < 0.05 compared to C30 by paired t-test.

decreased to 12 mm Hg as coronary perfusion pressure fell. In five similar experiments, the initial LVEDP was 12.0 ± 0.5 mm Hg; cessation of coronary perfusion decreased LVEDP by 4.6 ± 0.7 to 7.4 ± 0.8 mm Hg (P < 0.005). At a larger left ventricular volume, LVEDP decreased by 7.3 ± 1.4 mm Hg from 29.1 ± 1.6 to 21.8 ± 2.2 mm Hg (P < 0.01) when coronary perfusion was transiently stopped. The relationships between aortic and diastolic pressure were linear with a slope of 0.43 ± 0.06 mm Hg LVEDP/10 mm Hg AoP when LVEDP was set initially at 10 mm Hg, and with a slope of 0.7 ± 0.15 mm Hg LVEDP/10 mm Hg AoP when LVEDP was set initially at 30 mm Hg. The difference between these slopes was statistically significant (P < 0.05).

Effects of Adenosine Infusion on Ventricular Diastolic Compliance and Circumference

To delineate further the effect of alteration of coronary perfusion pressure and flow in the blood-perfused heart preparation, left ventricular filling curves were performed in a series of blood-perfused hearts instrumented with an epicardial segment length gauge and subjected to coronary adenosine infusion at constant flow or perfusion pressure; the results are shown.
perfusion pressure to 50 ± 4 mm Hg (P < 0.01) and only a slight decrease in coronary flow was observed as indicated by the shift to the right of the diastolic pressure-volume curve (A). When coronary flow was held constant, the adenosine infusion caused a decrease in coronary perfusion pressure to 50 ± 4 mm Hg (P < 0.01) and only a slight decrease in left ventricular diastolic chamber stiffness as indicated by the shift to the right of the diastolic pressure-volume curve (B). (*P < 0.05 vs. control value (O) by paired t-test).

Discussion

These observations in the buffer-perfused heart are similar to those reported above in the buffer-perfused hearts and demonstrate the "hydraulic" effect of the coronary vasculature in both experimental preparations.

These results show that total global ischemia caused a decrease in left ventricular diastolic wall thickness, a decrease in epicardial diastolic circumference, and an increase in ventricular diastolic compliance manifested as a shift to the right with decreased slope of the diastolic pressure-volume curve. These changes were not accompanied by a measurable change in the diastolic shape of the heart during ischemia. The effect of decreasing coronary perfusion to decrease ventricular diastolic pressure was more pronounced when hearts were on the steeper portion of the pressure-volume curve (i.e., at larger intraventricular volumes) and when stiffness had been increased by exposure of the hearts to prolonged ischemia and reperfusion. Conversely, increased coronary flow, which occurred during adenosine infusions at constant perfusion pressure, and upon switching from constant aerobic flow to constant pressure hypoxia, resulted in increased epicardial diastolic circumference at each ventricular volume and a shift to the left in the diastolic pressure-volume curve, indicating an increase in diastolic chamber stiffness.

Myocardial wall thickness is an important determinant of ventricular diastolic compliance (Grossman and McLaurin, 1976). The changes in ventricular compliance which we observed with increasing or decreasing coronary flow are probably related to changes in diastolic wall thickness determined by the volume of fluid contained in the coronary vascular compartment of the myocardium. Morgenstern et al. (1973) have shown that increasing perfusion pressure or flow increases coronary vascular volume and ventricular wall thickness. Acute ischemia presumably decreases coronary vascular volume and ventricular wall thickness and, hence, decreases wall stiffness. The changes we observed in diastolic wall thickness, epicardial diastolic segment length, and ventricular diastolic pressure occurred simultaneously with changes in coronary perfusion pressure (Fig. 6). This rapid time course makes it unlikely that the alterations in compliance were due to transudation of edema fluid between the vascular and extracellular compartments.

We had hypothesized that the increased diastolic stiffness and increased diastolic circumference seen during hypoxia at constant coronary flow were due to vasodilation and engorgement of the ventricular wall. However, the experiments with adenosine refuted this explanation (Fig. 4). Adenosine infusion at constant coronary flow caused a degree of vasodilation equal to that caused by hypoxia but had no significant effect on epicardial diastolic segment length or the diastolic pressure-volume curve. Thus it appears that the increased stiffness due to hypoxia at constant coronary flow is not related to the direct mechanical effects of coronary vasodilation and vascular engorgement, but may be due to the metabolic effects of tissue hypoxia resulting in incomplete relaxation. We drew the same conclusion when a similar result was obtained in experiments where intraventricular volume was held constant during hypoxia and adenosine coronary perfusion experiments (Serizawa et al., 1981).

The results of the present study clarify a number of previous observations. Salisbury et al. (1960) dem-
In the present experiments, coronary flow appeared to be a more important determinant of wall thickness and chamber stiffness than was perfusion pressure per se. This was observed in the experiments with adenosine in which wall thickness increased and compliance decreased when coronary flow was increased by adenosine at constant perfusion pressure but thickness and compliance remained virtually unchanged when perfusion pressure decreased at constant coronary flow. The relative importance of coronary pressure vs. flow as determinants of myocardial wall thickness and stiffness is controversial, as Morganstern et al. (1973) observed comparable effects of both pressure and flow on the geometry of the left ventricular wall, whereas Olsen et al. (1981) found a significant effect of perfusion pressure but not coronary flow on left ventricular compliance, this despite a two-fold increase of coronary flow with adenosine infusion. It seems likely that the direct determinant of the effect of coronary perfusion on diastolic ventricular pressure is coronary vascular volume. It is possible that pressure and flow make variable contributions to coronary vascular volume, depending on the perfusion rate and arterial tone. The experiments of Olsen et al. were performed in potassium-arrested hearts with low coronary flow rates (less than 1.0 ml/min per g), whereas the present experiments were performed at normal to above normal flow rates.

Several investigators have failed to observe an effect of coronary perfusion on ventricular diastolic pressure (Arnold et al., 1968; Abel and Reis, 1970; Templeton et al., 1972; Palacios et al., 1976; Foster et al., 1977). These studies generally involved smaller alterations of coronary flow or perfusion pressure than were used in our study or they were carried out on the lower, flat portion of the diastolic pressure-volume curve where we have seen the effect to be less marked. For example, Arnold et al. (1968) increased coronary perfusion pressure from 60 to 120 cm H2O in an isolated isovolumic balloon-in-left ventricular preparation similar to ours; initial LVEDP was set at the relatively low value of 2 mm Hg and was not significantly altered by the change in coronary perfusion pressure. Templeton et al. (1972) increased aortic perfusion pressure from 60 to 95 mm Hg and observed no effect on isovolumic LVEDP in the dog heart. Palacios et al. (1976) decreased coronary perfusion pressure from 80 to 50 mm Hg and saw no change in isovolumic LVEDP (which was set at the relatively low value of 8 cm H2O) in the dog. In other experiments, these workers (Palacios et al., 1976) measured the relationship between LVEDP and LVEDC (epicardial circumference) when coronary perfusion pressure was decreased from 75-95 to 40-60 mm Hg; the LVEDP-LVEDC relation was not changed, and these investigators concluded that LV diastolic stiffness was unchanged. However, the use of the epicardial circumferential gauge in a non-isovolumic ventricle (Palacios et al., 1976; Foster et al., 1977) may have summated two opposing effects, and reduced the sensitivity to detect any net effect: Any decrease in diastolic wall thickness would decrease epicardial circumference while a simultaneous increase in compliance would increase epicardial circumference at a given LVEDP. Thus, a modest reduction of coronary perfusion pressure may have caused...
opposite but balanced effects on the LVEDP-LVEDC relationship and resulted in a decrease in diastolic compliance nonetheless.

Several investigators have published diastolic pressure-volume curves for isolated blood-perfused hearts with changes in coronary perfusion pressure in the high to normal physiological range (Cross et al., 1961; Greuner-Sigusch et al., 1973; Olsen et al., 1981). In these experiments, perfusion pressure was decreased from higher values of 120–150 mm Hg to moderate levels of 80–90 mm Hg; as a result, left ventricular diastolic pressures decreased by about 2–3 mm Hg from initial values of 10 mm Hg. The magnitude of this response is quite consistent with the relationship which we observed in our blood-perfused hearts of a 0.4 mm Hg change in LV diastolic pressure per 10 mm Hg change in aortic pressure. Under these conditions, a 25–50 mm Hg change in coronary perfusion pressure would be required to effect a change of 1–2 mm Hg in LVEDP. It is not clear why Abel and Reis (1970), who increased coronary perfusion pressure from 75 to 150 mm Hg in isovolumic dog hearts, observed no effect on LVEDP, since the change in perfusion pressure was as great or greater than in the present study and those of Cross et al. (1961), Greuner-Sigusch et al. (1972), or Olsen et al. (1981). In addition to changes in position of the diastolic pressure-volume curve with changes in perfusion, we also observed changes in the slope of this relation (Table 1). A similar result was observed by Olsen et al. (1981), who calculated elastic coefficients by fitting pressure-volume data to an exponential curve.

Our results indicate a definite and significant coronary vascular hydraulic or “erectile” effect with relatively large changes in coronary perfusion. This effect was greater when the ventricle was stiffer (at larger diastolic volumes or after ischemic damage). Our study may have several clinical implications. The direct relationship which we have shown between coronary perfusion and diastolic ventricular stiffness could contribute to an increase in ventricular stiffness and LVEDP during an acute hypertensive crisis. Conversely, the direct effect of coronary perfusion on ventricular stiffness may contribute to the increase in left ventricular diastolic compliance observed during afterload reduction with nitroprusside or other similar agents (Brodie et al., 1977). It has been shown that an intact pericardium is required to observe a shift in position of the ventricular diastolic pressure-volume curve with nitroprusside (Shirato et al., 1978). The restraining influence of the pericardium may serve to amplify combined effects of altered right ventricular chamber volume and left ventricular wall thickness on left ventricular compliance after systemic vasodilation. The decrease in regional coronary perfusion which occurs after a coronary artery occlusion may contribute to the early increase in diastolic compliance which occurs in an acutely ischemic or infarcting myocardial region (Forrester et al., 1972; Tyberg et al., 1974; Theroux et al., 1974; Pirzada et al., 1976; Vokonas et al., 1976). The effect of coronary perfusion on ventricular diastolic stiffness may also contribute to the acute exacerbation of myocardial contracture observed during reperfusion after experimental global ischemia (Apstein et al., 1977; Gaasch et al., 1978; Vogel et al., 1980). Because the effect of coronary perfusion on the ventricular diastolic pressure-volume relationship was greater when diastolic chamber stiffness was increased, any clinically relevant effects of coronary perfusion on ventricular diastolic compliance might be more pronounced in subjects with volume overload (operating on the steep portion of the pressure-volume curve), or with increased ventricular stiffness due to cardiac disease (Grossman and Barry, 1980) such as, hypertrophy, cardiomyopathy, and chronic myocardial ischemia, or during recovery from surgical ischemic cardiac arrest (Chitwood et al., 1979; Spotnitz et al., 1979).

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