Coronary Pressure-Flow Relations in Hypertensive Left Ventricular Hypertrophy

Comparison of Intact Autoregulation With Physiological and Pharmacological Vasodilation in the Dog

Richmond W. Jeremy, Peter J. Fletcher, and John Thompson

Coronary pressure-flow relations during autoregulated and vasodilated flow states were compared between eight dogs with renovascular hypertension and left ventricular hypertrophy and 12 normal dogs. Each relation was constructed from serial steady-state measurements of end-diastolic coronary pressure and flow during perfusion of the circumflex artery by an extracorporeal circuit at controlled diastolic pressures of 20–200 mm Hg. Autoregulated pressure-flow relations were compared at three levels of myocardial oxygen demand: resting, high (dobutamine 10 μg/kg/min), and low (propranolol 2.5 μg/kg/min). Autoregulatory capacity was assessed by calculation of closed-loop flow gain. At each level of myocardial oxygen demand, the lower limit of autoregulation occurred at higher perfusion pressures in the hypertrophy group (rest 65±3, high 92±4, low 66±4 mm Hg) than in the normal group (rest 53±2, p<0.05; high 75±5, p<0.05; low 51±3 mm Hg) (p<0.05). Maximum autoregulatory gain was similar in the normal and hypertrophy groups during resting and low myocardial oxygen demand but was reduced in the hypertrophy group during dobutamine studies. When coronary flow decreased below the lower limit of autoregulation, systolic shortening was reduced in both normal and hypertrophy groups. However, as the autoregulatory limits were at higher pressures in the hypertrophy group, shortening in this group deteriorated at perfusion pressures that did not affect the normal heart. Coronary pressure-flow relations during physiological (peak hyperemia after 15-second flow occlusion) and pharmacological (intracoronary adenosine 400 μg/min) vasodilation was curvilinear and fitted by quadratic regression. During hyperemic vasodilation, maximal conductance per unit mass of myocardium was less in the hypertrophy group over a wide range of perfusion pressures. At a diastolic perfusion pressure of 80 mm Hg, maximum conductance was 4.6±0.5 ml/min/100 g/mm Hg in the normal group and 3.4±0.4 ml/min/100 g/mm Hg (p<0.05) in the hypertrophy group. Intracoronary adenosine elicited further vasodilation in both groups, but maximum conductance remained less in the hypertrophy group (8.5±1.7 ml/min/100 g/mm Hg at a perfusion pressure of 80 mm Hg) than in the normal group (13.5±2.0 ml/min/100 g/mm Hg) (p<0.05). Maximal coronary flow reserve is reduced in left ventricular hypertrophy, with a consequent shift of the lower limit of autoregulation to higher perfusion pressures. Thus, as coronary perfusion pressure is decreased, coronary flow and myocardial shortening become impaired at higher pressures in the hypertrophied heart than in the normal heart. (Circulation Research 1989;65:224–236)

Increased ventricular external load, such as systemic arterial hypertension, results in increased systolic wall stress and, thus, may be a stimulus to development of left ventricular hypertrophy.

Concentric hypertrophy, with an increased mass/volume ratio in proportion to the systolic pressure load, can limit increases in wall stress in the presence of arterial hypertension. Consequently, myocardial oxygen consumption and coronary flow requirements per unit mass of myocardium may return toward normal despite persistence of high external load. Experimental studies indicate that resting coronary flow per unit mass of myocardium is normal in the hypertrophied left ventricle. Further, during moderate increases in ventricular work, such as pacing or exercise, similar increases
in coronary flow have been found in normal and hypertrophied ventricles, although lower myocardial blood flow has been noted during rapid pacing in the hypertrophied heart. These findings suggest that autoregulation of coronary flow persists in the presence of hypertrophy.

In contrast to the findings regarding autoregulated coronary flow, considerable evidence indicates that maximal coronary flow reserve per unit mass of myocardium is reduced in the hypertrophied heart. Thus, during physiological coronary vasodilation induced by rapid pacing, subendocardial hypoperfusion and net myocardial lactate production have been observed. Similarly, coronary flow during postocclusion hyperemia is lower in hypertrophied hearts than in normal hearts. Studies of pharmacological coronary vasodilation have also found lower maximal coronary flow per unit mass in the hypertrophied myocardium. Thus, both physiological and pharmacological coronary flow reserve per unit mass of myocardium appear to be impaired in left ventricular hypertrophy.

The lower limits of autoregulation of coronary flow are largely determined by the slope of the coronary pressure-flow relation during maximal physiological vasodilation. As a result, when resting coronary flow increases, the lower limit of autoregulation is shifted to higher perfusion pressures. As proposed by Hoffman and by Klocke, another consequence of this relation is that a reduction in the slope of the vasodilated pressure-flow relation would also shift the lower limits of coronary autoregulation to higher pressure levels. The evidence of reduced coronary flow reserve due to lower maximal coronary conductance in the hypertrophied heart, therefore, suggests that the lower limits of autoregulation should be shifted to higher perfusion pressures in those hearts. To date, however, complete autoregulated coronary pressure-flow relations have not been described in hypertrophied hearts, and the expected shift in the limits of autoregulation has not been documented experimentally.

This study compared both autoregulated and maximally vasodilated coronary pressure-flow relations between normal dogs and dogs with left ventricular hypertrophy secondary to systemic arterial hypertension. Autoregulated pressure-flow relations were recorded over a wide range of perfusion pressures at three different levels of myocardial oxygen demand to document the limits of autoregulation. Coronary pressure-flow relations during maximal physiological and pharmacological vasodilation were compared as a measure of coronary flow reserve in normal and hypertrophied hearts.

**Study Group**

Experiments were performed in 20 male mongrel dogs weighing 15–25 kg. Twelve dogs were normal, and eight had left ventricular hypertrophy secondary to chronic renovascular hypertension.

**Renovascular Hypertension and Left Ventricular Hypertrophy**

Dogs were conditioned in the animal house for 2 weeks before operation. After induction of anesthesia with thiopentone sodium (15 mg/kg i.v.), the dogs breathed a mixture of nitrous oxide (4 l/min), oxygen (2 l/min), and halothane (0.5–1.5%). Under sterile conditions, bilateral flank incisions were made. A Doppler flow probe (Titronics Inc, Oxford, Iowa) and balloon occluder (5 mm i.d.) (Hazen Everett, Teaneck, New Jersey) were placed around the left renal artery, and the right kidney was removed. A polyvinyl catheter (0.86 mm i.d., 1.52 mm o.d.) was advanced to the descending aorta for 5 cm via the right renal artery for arterial pressure measurement. This catheter was filled with sodium heparin 5,000 units/ml and tunneled subcutaneously, with the flow probe leads and balloon inflation catheter, to the back of the neck. On completion of the operation, intramuscular benzathine penicillin G was administered and the dogs were returned to the recovery cages. The dogs were observed frequently during the postoperative period, and analgesia (Fentanyl, 1–2 µg/kg intramuscular injection as required) (Elkins-Sinn, Cherry Hill, New Jersey) was administered to each dog to reduce postoperative discomfort.

After recovery from surgery, arterial blood pressure (Statham model P23AC, Gould Inc, Cleveland) and renal artery flow (Doppler flowmeter, Iowa State University Bioengineering Department, Ames, Iowa) were measured daily while the dogs lay quietly without restraint on a low table. The renal artery balloon was gradually inflated over 2–3 weeks, according to the change in renal artery flow and arterial pressure, for induction of stable systemic hypertension. The dogs were then monitored with systemic hypertension for a mean duration of 9 weeks (range 6–12 weeks) before hemodynamic study.

**Hemodynamic Instrumentation**

On the day of study, the dogs were anesthetized with pentobarbital sodium (30 mg/kg i.v.), and supplemental doses (15 mg/kg) were given as required. The dogs were intubated and ventilated with air and oxygen (model 613A, Harvard Apparatus, South Natick, Massachusetts) at a tidal volume of 15 ml/kg body weight. Arterial oxygen saturation was greater than 95% throughout the experiment, and end-expired PCO2 was maintained at between 30 and 40 mm Hg by use of a Normocap monitor (Datex Instrumentation, Helsinki, Finland). Rectal temperature was kept at 37°–38° C by heating lamps under the experimental table; lead III of the electrocardiogram was monitored throughout the procedure.

A polyvinyl catheter (1.5 mm o.d.), advanced to the inferior vena cava via the left femoral vein, was...
used for administration of drugs. Another catheter (2.0 mm i.d., 3.0 mm o.d.) was placed in the left femoral artery and connected to an extracorporeal perfusion circuit. A polyethylene catheter (0.86 mm i.d., 1.52 mm o.d.) was advanced to the ascending aorta via the right common carotid artery for measurement of systemic arterial pressure. Another catheter (2.0 mm i.d., 3.0 mm o.d.) was advanced to the right atrium via the right external jugular vein and connected to an external venous reservoir, while right atrial pressure was measured by a small (0.28 mm i.d., 0.58 mm o.d.) intraluminal catheter.

After thoracotomy in the fifth left intercostal space, the heart was suspended in a pericardial cradle. Left atrial pressure was measured by a catheter (2.0 mm i.d., 3.0 mm o.d.) introduced through the appendage; left ventricular pressure was measured via a 5-cm polyethylene catheter (0.86 mm i.d., 1.52 mm o.d.) introduced by an apical puncture and connected directly to a solid-state transducer (model PC-350, Millar, Houston, Texas). Left ventricular dp/dt was recorded by analog differentiator (model TP20, Grass Instrument, Quincy, Massachusetts). Systolic myocardial shortening was measured by a pair of piezoelectric crystals placed in the subendocardium approximately 10 mm apart in diastole and oriented parallel to the short axis of the left ventricle. Regional dimensions were continuously recorded by a pulse-transit sonomicrometer (model 401, Schuessler Associates, Cardiff-by-the-Sea, California). Segment lengths were measured at end-diastole (EDD, onset of positive left ventricular dp/dt) and end-systole (ESD, onset of negative dp/dt), and shortening was calculated as (EDD-ESD)/EDD. Placement of the crystals wholly within the perfused circumflex myocardium was verified at the end of each experiment by staining of the circumflex territory with saturated crystal violet solution. All catheters were filled with heparinized saline (50 IU/ml) and connected to Statham Model P23Db transducers (Gould) for pressure measurement. The midheart level was used as the zero reference. Data were recorded on an eight-channel polygraph (model 7D, Grass Instruments) and FM tape recorder (model 3968A, Hewlett-Packard, Palo Alto, California).

**External Venous Reservoir**

An external venous reservoir, primed with fresh heparinized blood (5,000 IU/l) from a donor dog, was used to compensate for blood withdrawn to the coronary perfusion circuit and to maintain constant intravascular volume throughout the experiment, as changes in left ventricular end-diastolic pressure may alter the coronary zero-flow pressure. An outflow line from the reservoir passed through a roller pump (model 4504, Drake-Willock, Portland, Oregon) and was connected to the right atrial catheter by a three-way connector before returning to the reservoir. Blood was continuously recirculated by the pump and infused or withdrawn from the experimental dog as necessary to maintain constant left ventricular end-diastolic pressure. Left ventricular end-diastolic pressure was easily maintained at 10–12 mm Hg throughout the experiment as long as rapid inflow or outflow of blood from the coronary perfusion circuit was avoided.

**Coronary Perfusion Circuit**

The circumflex artery was perfused at controlled pressures by an extracorporeal circuit, which has been previously described in detail. Oxygenated blood was pumped (model BP-3B, Gambro, Lund, Sweden) from the left femoral artery to a pressurized flask. Pump speed was continuously adjusted to maintain 150–200 ml of blood in the flask, which was immersed in a heated water bath and pressurized with oxygen from a high-pressure source. The flask pressure was regulated by mercury manometers, which controlled electromagnetic oxygen bleed valves, so that a stable coronary perfusion pressure was maintained. Dual pressure channels were employed to facilitate step changes in coronary perfusion pressure.

Blood leaving the pressurized flask passed through a microaggregate filter (model SQ405, Pall Biomedical, Ulitipor, East Hills, New York) and a cannulating electromagnetic flow probe (model EP 300AP and Flowmeter 501A, Carolina Medical Electronics, King, North Carolina) before entering the circumflex artery through a stainless steel cannula (25 mm long, 1.8 mm i.d., 1.9 mm o.d.). The electromagnetic flow probe was calibrated by perfusion with blood at known flow rates before the experiment. Inflow pressure to the circumflex artery was measured at the tip of the coronary cannula by a fine (0.28 mm i.d., 0.58 mm o.d.) fluid-filled catheter, placed within the perfusion line with the tip just outside the end of the cannula and connected to a Statham P23Db transducer (Gould).

After dissection of the proximal circumflex artery, the coronary perfusion circuit was primed with blood, and 5,000 units sodium heparin was given intravenously. The proximal circumflex artery was then ligated, and the steel cannula was introduced via a small arteriotomy. The median ischemia time was 55 seconds (range 26–150 seconds). Immediately after cannulation, the circumflex territory was perfused at a diastolic pressure of 100 mm Hg, and regional myocardial shortening rapidly recovered to precannulation levels. Autonomic effects associated with anesthesia were attenuated by trimethaphan camsylate (Arfonad, Hoffmann la Roche, Basel, Switzerland), with the intravenous infusion (5–10 μg/kg/min) titrated to limit the pressor response after bilateral carotid occlusion to less than a 10 mm Hg increase in mean arterial pressure. Transient coronary vasodilation, similar to that previously described, was sometimes observed at the start of the trimethaphan infusion, but this vasodilation dissipated over 30 minutes. A recovery
period of 1 hour was always allowed before data collection began.

**Experimental Protocol**

Similar study protocols were employed in each of the normal and hypertrophied hearts. Initial studies of coronary autoregulation were made during resting myocardial oxygen demand. Coronary flow reserve during physiological (postocclusion hyperemia) and pharmacological (intracoronary adenosine) vasodilation was then measured. After return of coronary flow to resting levels (recovery time 15–20 minutes), coronary autoregulation was assessed during high and low myocardial oxygen demand.

**Autoregulated Pressure-Flow Relations**

After the resting studies, myocardial oxygen demand was increased by dobutamine (10 μg/kg/min i.v.), and autoregulatory studies were repeated. Finally, myocardial oxygen demand was reduced by propranolol (2.5 μg/kg/min for 10 minutes, then 0.25 μg/kg/min), and a third set of autoregulatory pressure-flow data was obtained. At each level of myocardial oxygen demand, the circumflex territory was perfused at steady-state diastolic pressures between 30 and 240 mm Hg. Measurements of end-diastolic circumflex pressure and flow were made after coronary flow had been stable at each new pressure for at least 2 minutes. Eight to 12 pressure-flow pairs were obtained for each autoregulation curve at pressure increments of 15–20 mm Hg with the perfusion pressures selected in random order. Each autoregulation data set was fitted by a fourth-order polynomial regression (mean r² = 0.975, range 0.919–0.999). Coronary pressure-flow pairs were calculated from the regression equation for 10-mm Hg increments in diastolic coronary perfusion pressure, and autoregulatory gain was calculated for each 10-mm Hg pressure increment according to the formula

\[
\text{Gain} = 1 - \left[ \frac{(dQ/Q)}{(dP/P)} \right]
\]

where \( dQ \) is the change in flow after a given change in perfusion pressure \( dP \) from a reference pressure-flow point \( (P, Q) \). For each dog, autoregulatory gain was plotted against coronary perfusion pressure at each level of myocardial oxygen demand. The limits of autoregulation were considered to be exceeded when the gain value was zero or less.

The reproducibility of diastolic coronary pressure-flow measurements with intact autoregulation during resting myocardial oxygen demand was assessed in preliminary studies in five normal dogs. Diastolic coronary flow was initially measured at a perfusion pressure of 100 mm Hg before measurements of autoregulated flow were made at randomly chosen perfusion pressures of 30–240 mm Hg over a period of 30–45 minutes. Diastolic perfusion pressure was then restored to 100 mm Hg, and flow was recorded. Measurement of a series of autoregulated pressure-flow points was then repeated over a similar range of pressures. Diastolic flow at a perfusion pressure of 100 mm Hg was 1.8±0.3 ml/min/g for the first autoregulation series and 1.7±0.3 ml/min/g for the second series. The lower limits of autoregulation were similar for the first (48±5 mm Hg) and second (50±5 mm Hg) series. The upper limits of autoregulation were 165±9 mm Hg for the first series and 162±7 mm Hg for the second series.

**Vasodilated Pressure-Flow Relations**

Vasodilated coronary pressure-flow relations were studied during a state of resting myocardial oxygen demand. Physiological vasodilation was induced by coronary flow occlusion. The circumflex territory was perfused at a diastolic pressure of 120 mm Hg for 2 minutes before flow was occluded for 15 seconds, during which a step change to a different coronary perfusion pressure was made. Flow occlusions of 15 seconds' duration result in maximal or near-maximal physiological coronary vasodilation. Coronary pressure and flow were measured continuously after release of the occlusion, and the point of maximum hyperemic conductance was determined as the beat with the peak ratio of end-diastolic flow and perfusion pressure. At the end of the hyperemia, diastolic coronary perfusion pressure was restored to 120 mm Hg for at least 2 minutes before the next flow occlusion. The pressure-flow relation was determined from a series of 10 to 12 measurements of end-diastolic coronary pressure and flow at peak hyperemia during perfusion at diastolic pressures between 20 and 160 mm Hg.

Subsequently, pharmacological vasodilation was induced by continuous intracoronary infusion of adenosine (400 μg/min), which resulted in prompt, maximal coronary vasodilation. The coronary pressure-flow relation was then determined from another 10 to 12 measurements of end-diastolic coronary pressure and flow during steady-state perfusion of the circumflex territory at diastolic pressures between 20 and 160 mm Hg. Maximal coronary vasodilation was confirmed by occlusion of circumflex flow for 15 seconds, which did not elicit any hyperemic response, and by infusion of adenosine at 800 μg/min, which did not further increase flow.

At the end of the experiment, the circumflex artery was perfused at the control pressure of 120 mm Hg diastolic, and a saturated solution of crystal violet stain was infused into the coronary line for delineation of perfused myocardium. After a lethal dose of pentobarbital sodium, the heart was excised and trimmed of epicardial fat, vessels, and valvular tissue. The right ventricular free wall was removed along the interventricular grooves, and the ventricles were weighed separately. The perfused circumflex territory was divided from the remainder of the left ventricle and weighed.
TABLE 1. Hemodynamic Parameters During Autoregulation of Coronary Flow at Three Levels of Myocardial Oxygen Demand in Normal and Hypertrophied Hearts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dobutamine</th>
<th>Rest</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>Normal</td>
<td>156±7*</td>
<td>130±5</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>181±12‡</td>
<td>138±7</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>Normal</td>
<td>161±8*</td>
<td>135±5</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>192±14‡</td>
<td>175±6§</td>
</tr>
<tr>
<td>Double product (mm Hg/min)/10^6</td>
<td>Normal</td>
<td>257±15†</td>
<td>179±9</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>352±41†</td>
<td>289±264†</td>
</tr>
<tr>
<td>LV diastolic pressure (mm Hg)</td>
<td>Normal</td>
<td>10±1</td>
<td>11±1</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>10±1</td>
<td>11±1</td>
</tr>
<tr>
<td>LV dP/dt max (mm Hg/sec)</td>
<td>Normal</td>
<td>5,136±622*</td>
<td>2,458±163</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>5,588±424*</td>
<td>2,613±208</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
LVH, left ventricular hypertrophy; LV, left ventricle.
*p<0.05 vs. rest.
‡p<0.01 vs. rest.
*‡p<0.05 vs. normal group.
§p<0.01 vs. normal group.

Statistical Analysis

Hemodynamic parameters and coronary flow at each level of myocardial oxygen demand were compared within each group by analysis of variance,26 and between groups by Student's t test. The relations between autoregulated coronary flow and the double product (heart rate x peak left ventricular systolic pressure) were determined in each of the normal and hypertrophy groups by linear regression and compared between groups by analysis of covariance. Comparisons of perfusion-pressure limits of autoregulation between normal and hypertrophy groups at each level of myocardial oxygen demand were made by Student's t test. Vasodilated coronary pressure-flow relations were curvilinear and thus were fitted by quadratic regression and extrapolated to the diastolic zero-flow pressure. Coronary conductance at each level of perfusion pressure was determined by calculation of the slope of the pressure-flow relation. Results were expressed as mean±SEM, and p<0.05 was regarded as statistically significant.

Results

The mean body weight of the hypertensive group before any surgical intervention (22.6±1.6 kg) did not change by the time of study (22.7±1.4 kg) and did not differ from that of the normal dogs (23.3±0.9 kg). Mean left ventricular weight in the hypertensive group (5.47±0.17 g/kg) was significantly greater than in the normal group (4.05±0.10 g/kg) (p<0.01).

Autoregulated Pressure-Flow Relations

The principal hemodynamic parameters during measurement of autoregulated pressure-flow relations are shown in Table 1. In both groups the major determinants of myocardial oxygen demand increased during dobutamine infusion and decreased during propranolol infusion. Left ventricular systolic pressure and the double product were higher in the hypertrophy group at rest and during high myocardial oxygen demand. Left ventricular dP/dt max and diastolic pressure were similar in the two groups.

Autoregulation of coronary flow was evident in each dog in the normal and hypertrophy groups at the three levels of myocardial oxygen demand. Data from a representative dog with left ventricular hypertrophy are shown in Figure 1, together with the fitted polynomial regressions and the width of the autoregulatory range at each level of oxygen demand. The observed pressure-flow data are well fitted by the regression. As myocardial oxygen demand increased, the width of the autoregulatory range decreased and the lower limit of autoregulation shifted to higher perfusion pressures.

At the diastolic perfusion pressure in the center of the autoregulatory range, coronary flow (Q) was similar in the normal and hypertrophy groups at each level of myocardial oxygen demand (Table 2, range center) and was directly related to prevailing myocardial oxygen demand, indexed by the double product (DP): normal, Q = 0.00937 x DP - 0.19 ml/min/g (r=0.73); hypertrophy, Q = 0.00491 x DP + 0.16 ml/min/g (r=0.67). The slope of the relation for the hypertrophy group was lower than that for the normal group (p<0.01).

The relations between coronary perfusion pressure and mean autoregulatory gain at each level of myocardial oxygen demand are shown for the normal and hypertrophy groups in Figure 2. During resting myocardial oxygen demand, the normal group exhibited mean gain values greater than zero at diastolic perfusion pressures between 53 and 159
mm Hg with a maximum gain of 0.92±0.03. In the hypertrophy group, the gain curve was shifted to the right, with a lower autoregulatory limit of 65 mm Hg and a maximum gain of 0.88±0.06 (p=NS vs. normal). During high oxygen demand, a mean gain greater than zero was observed at perfusion pressures between 75 and 155 mm Hg in the normal group, with a maximum gain of 0.82±0.06 (p=NS vs. rest). The gain curve in the hypertrophy group was again shifted to the right, with a lower limit of 92 mm Hg. Maximum gain was 0.49±0.09, which was significantly less than in the normal group (p<0.05 vs. normal). During low myocardial oxygen demand, maximum gain was similar in the normal (0.83±0.07) and hypertrophy (0.81±0.07) groups, but the gain curve in the hypertrophy group exhibited negative values at perfusion pressures below 67 mm Hg, compared with 52 mm Hg in the normal group.

The limits of autoregulation of diastolic coronary flow, calculated from individual flow gain curves, at each level of myocardial oxygen demand are summarized in Table 2. In both normal and hypertrophied hearts, the lower limit of autoregulation increased as myocardial oxygen demand increased. However, at each level of myocardial oxygen demand, the lower limit of autoregulation occurred at significantly higher perfusion pressures in the hypertrophy group. The upper limits of autoregulation also tended to occur at higher perfusion pressures in the hypertrophy group, but the differences were not significant. The width of the autoregulatory range was similar in the normal and hypertrophy groups during resting and low oxygen demand. However, during high oxygen demand, the width of the autoregulatory range was reduced in both groups,

<table>
<thead>
<tr>
<th>Table 2. Autoregulatory Ranges for Diastolic Coronary Flow in Normal and Hypertrophied Hearts at Three Levels of Myocardial Oxygen Demand</th>
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<tbody>
<tr>
<td>Dobutamine</td>
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<tr>
<td>Lower limit</td>
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<tr>
<td>P (mm Hg)</td>
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<tr>
<td>Q (ml/min/g)</td>
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<tr>
<td>Range center</td>
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<tr>
<td>P (mm Hg)</td>
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<tr>
<td>Q (ml/min/g)</td>
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<tr>
<td>Upper limit</td>
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<td>P (mm Hg)</td>
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<td>Q (ml/min/g)</td>
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<tr>
<td>Range width (mm Hg)</td>
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<tr>
<td>Hypertrophy Group</td>
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<tr>
<td>Lower limit</td>
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<td>P (mm Hg)</td>
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<td>Q (ml/min/g)</td>
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<tr>
<td>Range center</td>
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<td>Q (ml/min/g)</td>
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<tr>
<td>Upper limit</td>
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<tr>
<td>P (mm Hg)</td>
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<tr>
<td>Q (ml/min/g)</td>
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<tr>
<td>Range width (mm Hg)</td>
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</tbody>
</table>

Values are mean±SEM.
P, diastolic perfusion pressure; Q, diastolic coronary flow.
* p<0.01 vs. rest.
†p<0.05 vs. rest.
‡p<0.05 vs. normal group.
with the range in the hypertrophy group being significantly less than in the normal group.

**Perfusion Pressure and Systolic Shortening**

The functional significance of the shift in the lower limit of autoregulation in the hypertrophy group is underscored by the relation between perfusion pressure and regional myocardial shortening (Figure 3). Systolic shortening at each level of myocardial oxygen demand is shown at similar perfusion pressures in normal and hypertrophied hearts. During resting myocardial oxygen demand, in the normal group, shortening was maintained as perfusion pressure decreased to 54±2 mm Hg, which is similar to the lower limit of autoregulation (53±2 mm Hg). When diastolic perfusion pressure was reduced further to 34±2 mm Hg, shortening decreased from 17.9±1.1% to 10.1±1.3% (p<0.01). In contrast, in the hypertrophy group, shortening was maintained only at perfusion pressures down to 67±2 mm Hg (shortening=15.5±2.0%, p=NS vs. normal), the lower limit of flow autoregulation being 65±3 mm Hg. When diastolic perfusion pressure was further reduced to 51±2 mm Hg, regional shortening decreased to 10.9±1.2% (p<0.05). A similar relation between the lower limit of flow autoregulation and impairment of regional shortening in the hypertrophy group was also found during high myocardial oxygen demand. In the normal hearts, shortening of 19.1±0.75% was observed at a diastolic perfusion pressure of 76±2 mm Hg, but shortening decreased to 14.9±0.6% (p<0.05) when perfusion pressure was reduced to 49±3 mm Hg. In the hypertrophy group, systolic shortening of 16.0±1.5% at a perfusion pressure of 93±4 mm Hg decreased to 12.0±1.4% (p<0.05) when perfusion pressure was reduced to 74±1 mm Hg. During low myocardial oxygen demand, there was a small, but not significant, reduction in shortening during perfusion at the lowest pressures in each group. Thus, in accord with the rightward shift of the lower limits of coronary flow autoregulation, regional shortening is impaired in the hypertrophied heart during perfusion at diastolic pressures that do not adversely affect the normal heart.

**Vasodilated Pressure-Flow Relations**

**Physiological vasodilation.** Hemodynamic parameters during the preocclusion perfusion period are shown for the normal and hypertrophy groups in Table 3. The major difference between the groups was the higher peak left ventricular systolic pressure in the hypertrophy group. In both groups, diastolic pressure-flow relations exhibited curvature, convex to the pressure axis, at low perfusion pressures, and these relations were better fitted by quadratic regression (r²=0.99±0.003) than by linear regression (r²=0.97±0.003, p<0.05). The diastolic pressure-flow relations during physiological vasodilation are compared between normal and hypertrophy groups in Figure 4. The relations between perfusion pressure and total circumflex flow (Figure 4A) were similar in the two groups, but flow per unit mass of myocardium (Figure 4B) was significantly reduced in the hypertrophy group over a wide range of perfusion pressures. There was no difference in calculated diastolic zero-flow pressure between the normal (17.6±2.6 mm Hg) and hypertrophy (18.5±2.0 mm Hg) groups. Diastolic coronary conductance increased as perfusion pressure increased in both groups. Although total diastolic conductance was similar in the two groups, conductance per unit mass of myocardium at a given perfusion pressure was significantly lower in the hypertrophy group than in the normal group. At diastolic perfusion pressures of 40–120 mm Hg, which encompass the lower pressure limits of autoregulation, mean diastolic conductance per 100 g of myocardium in the hypertrophy group was only 70% of that of the normal group. As the relative mass of the hypertrophied hearts was 1.35 times that of the normal hearts, it is of note that the
relative conductance in the hypertrophied hearts (0.70) was very similar to the reciprocal of the increase in mass (0.74).

Pharmacological vasodilation. Hemodynamic parameters prevailing during the intracoronary infusion of adenosine are summarized in Table 3. As with the physiological series, peak left ventricular systolic pressure was higher in the hypertrophy group, while other parameters were similar in the two groups. During pharmacological vasodilation, diastolic pressure-flow relations were also curvilinear and well fitted by quadratic regression ($r^2=0.99\pm0.003$ in each group). Diastolic pressure-flow relations for the two groups are illustrated in Figure 5. Total circumflex flow (Figure 5A) during the adenosine infusion was similar in the normal and hypertrophied hearts and exceeded flow during physiological vasodilation in both groups. However, flow per unit mass (Figure 5B) of myocardium remained significantly lower in the hypertrophy group over a wide range of perfusion pressures. The diastolic zero-flow pressures were similar to those during physiological vasodilation (normal 17.8±1.5 mm Hg, hypertrophy 15.2±2.3 mm Hg, $p=NS$). Diastolic coronary conductance during maximal pharmacological vasodilation was greater than maximal physiological conductance in both normal and hypertrophied hearts (Table 4), but a significantly lower maximal conductance per unit mass of myocardium was still observed in the hypertrophy group. Maximal diastolic conductance per 100 g in the hypertrophy group was 63% of that in the normal group.

Discussion

The principal findings of this study are that although autoregulation of coronary flow persists in the hypertrophied heart, autoregulatory capacity is less than in the normal heart. The lower limit of autoregulation is shifted to higher perfusion pressures, so that coronary flow and myocardial function become impaired at perfusion pressures that do not adversely affect...
FIGURE 4. Relations between diastolic coronary pressure (P) and flow (Q) at peak hyperemia following 15-second coronary flow occlusion. Quadratic regressions refer to pooled data for each group. Panel A: Total diastolic circumflex flow is similar in normal and hypertrophied hearts at each perfusion pressure. For normal group, $Q=0.00551P^2+1.65P-32.5$ ml/min ($r^2=0.999$). For hypertrophy group, $Q=0.0017P^2+2.13P-48.7$ ml/min ($r^2=0.999$). Panel B: Flow per unit mass of myocardium is significantly less in hypertrophied hearts over a wide range of perfusion pressures. For normal group, $Q=0.00010P^2+0.029P-0.56$ ml/min/g ($r^2=0.999$). For hypertrophy group, $Q=0.00006P^2+0.025P-0.57$ ml/min/g ($r^2=0.999$). *p<0.05 vs. normal group at similar perfusion pressure.

the normal heart. During high myocardial oxygen demand, the lower limit of autoregulation in the hypertrophied heart may approach normal diastolic coronary perfusion pressures. The shift in the lower limit of autoregulation reflects reduced maximal diastolic coronary conductance per unit mass of myocardium during physiological vasodilation in the hypertrophied heart. Despite this limitation of phys-

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<th>Table 4. Coronary Perfusion Pressure and Flow During Postocclusion Hyperemia and During Intracoronary Adenosine in Normal and Hypertrophy Groups</th>
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<td><strong>Diastolic coronary perfusion pressure</strong></td>
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<td>40 (mm Hg)</td>
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<tr>
<td><strong>Hyperemia</strong></td>
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<td>LC total flow (ml/min)</td>
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<td><strong>Adenosine</strong></td>
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Values are mean±SEM.
LC, left circumflex; LVH, left ventricular hypertrophy.
*p<0.05 vs. normal group.
†p<0.05 vs. hyperemia.
‡p<0.01 vs. hyperemia.
Figure 5. Relations between diastolic coronary pressure (P) and flow (Q) during maximal vasodilation with adenosine. Regressions are for pooled data of the groups. Panel A: Total circumflex flow exceeds that during physiological vasodilation and is similar in normal and hypertrophied hearts. For normal group, $Q = 0.0402P^2 + 1.32P - 23.8$ ml/min ($r^2 = 0.999$). For hypertrophy group, $Q = 0.0392P^2 + 1.09P - 24.3$ ml/min ($r^2 = 0.999$). Panel B: Flow per unit mass of myocardium remains significantly lower in hypertrophied hearts despite further vasodilation with adenosine. For normal group, $Q = 0.00085P^2 + 0.0063P - 0.15$ ml/min/g ($r^2 = 0.999$). For hypertrophy group, $Q = 0.00049P^2 + 0.0145P - 0.31$ ml/min/g ($r^2 = 0.999$). *p < 0.05 vs. normal group at similar perfusion pressure.

Physiological flow reserve, the hypertrophied heart does possess an additional pharmacological flow reserve, similar to that found in normal hearts.

Critique of Methods

The degree of left ventricular hypertrophy produced in this study is similar to that documented in other studies of dogs with renovascular hypertension or perinephritic hypertension, although aortic banding in puppies produces more severe hypertrophy. It is likely that the hypertrophy in the present group represents a stable response to increased ventricular afterload, since significant hypertrophy, with reduction of systolic wall stress, occurs within 3 weeks of pressure loading in dogs. Furthermore, the increase in left ventricular mass in dogs with systemic hypertension is similar, whether the hypertension is of 6 weeks' or 6 months' duration.

This study employed controlled-pressure perfusion of the circumflex territory to obviate changes in myocardial oxygen demand during alteration of aortic pressure. Nonetheless, small changes in myocardial oxygen demand may occur when coronary perfusion pressure is increased (Gregg phenomenon) as a result of increased sarcomere length. However, in working hearts this effect appears to be slight at perfusion pressures below 120 mm Hg. Thus, characterization of the lower limits of autoregulation in this study is not likely to be greatly confounded by perfusion pressure-dependent changes in myocardial oxygen demand. Steady-state measurements of coronary pressure and flow were made at end-diastole to minimize capacitance-related errors in measurement of forward coronary flow. Recent work indicates that, at the heart rates studied in these experiments, systole does not appear to significantly impede diastolic coronary flow. Left ventricular diastolic pressure was also controlled, since left ventricular hypertrophy may be associated with increased diastolic filling pressures and the diastolic coronary zero-flow pressure is related to left ventricular diastolic pressure. Thus, increased left ventricular end-diastolic pressure could result in underestimation of coronary conductance in the hypertrophied heart, while associated subendocardial hypoperfusion would confound measurement of coronary flow and myocardial shortening at the lower limits of coronary flow autoregulation.

Measurements of circumflex artery flow may also be affected by collateral inflow from the left anterior...
Interpretation of Results

The limits of autoregulation were determined by use of the closed-loop flow gain, which has been employed in previous studies of autoregulation in both the mesenteric and coronary circulation. According to this formula, when the relative change in flow exceeds the relative change in perfusion pressure, the gain value is less than or equal to zero and autoregulatory capacity is considered to be exhausted. A gain value greater than zero indicates the presence of autoregulation, the degree of which can be assessed by how closely the gain approaches a value of 1. Autoregulatory studies were repeated during resting conditions and when myocardial oxygen demand was altered to a new steady state by continuous intravenous infusion of dobutamine or propranolol. Current evidence indicates that the direct pharmacological effect of these agents on the coronary vasculature is limited and is overridden by the dominant effect of myocardial metabolic state on coronary flow.

As with the autoregulated relations, vasodilated pressure-flow relations were determined during steady-state perfusion of the circumflex circulation to avoid capacitance effects associated with determination of relations during long diastoles with declining perfusion pressure. In this study, physiological coronary vasodilation was induced by 15-second flow occlusion, while other investigators have employed pacing tachycardia or exercise. The degree of vasodilation induced by physiological stimuli remained less than that induced by pharmacological agents. However, vasodilation induced by intracoronary infusion of adenosine appeared maximal, as a concurrent 15-second flow occlusion did not elicit any hyperemic response and coronary flow did not increase further when the rate of adenosine infusion was doubled. The infusion rate employed in this study is similar to that documented by other groups for induction of maximal coronary vasodilation in normal hearts.

The finding of similar levels of diastolic coronary flow in the normal and hypertrophy groups during intact autoregulation at each level of myocardial oxygen demand is in accord with previous studies. In both the normal and hypertrophy groups, there is a direct relationship between myocardial oxygen demand, indexed by the double product, and diastolic coronary flow, but the relation has a lower slope in the hypertrophy group. This is consistent with limitation of increases in wall stress in the hypertrophied heart, resulting in lower coronary flow requirements at each level of double product.

The present findings demonstrate that autoregulation of coronary flow persists over a wide range of perfusion pressures in the hypertrophied left ventricle, as has been previously suggested. The lower limit of autoregulation occurs at higher perfusion pressures as myocardial oxygen demand increases. However, at each level of myocardial oxygen demand, the lower limit of autoregulation, with an accompanying deterioration in regional shortening, occurs at higher diastolic perfusion pressures in the hypertrophied heart than in the normal heart. These results show that a reduction in coronary perfusion pressure, which may not compromise a normal heart, could cause ischemia in a hypertrophied heart even during conditions of resting myocardial oxygen demand.

The slope of the vasodilated pressure-flow relation is a principal determinant of the lower limit of the autoregulatory range of coronary flow. Impaired physiological flow reserve would result in a reduced slope of the vasodilated pressure-flow relation and a rightward shift of the autoregulatory limits. The shift in the lower limits of autoregulation observed in this study are consistent with this hypothesis, as maximal coronary conductance during reactive hyperemia after 15-second flow occlusion was reduced in the hypertrophied hearts. Although total circumflex flow at each level of perfusion pressure was similar in the normal and hypertrophy groups, maximal flow per unit mass of myocardium was significantly less in the hypertrophy group over a wide range of perfusion pressures. Several other studies support the presence of reduced physiological flow reserve in the presence of left ventricular hypertrophy.

Despite evidence of an impaired physiological coronary flow reserve, adenosine still elicited further coronary vasodilation in the hypertrophied hearts. The proportional increase in coronary flow with pharmacological vasodilation was similar in the normal and hypertrophied hearts but, in accord with previous studies, maximal coronary conductance per unit mass of myocardium remained less in the hypertrophy group. Thus, the discrepancy between physiological and pharmacological vasodilation, present in normal hearts, persists in the hypertrophied heart. This suggests that the hypertrophied heart is unable to recruit the additional flow reserve, or else that to do so would not usefully improve nutrient myocardial perfusion. It is of note that when regional myocardial shortening is impaired by perfusion at low coronary pressures, increasing coronary flow by exogenous vasodilators has not consistently been shown to improve myocardial contraction.
The present findings of reduced coronary flow reserve in the hypertrophied left ventricle are consistent with the hypothesis that there is a structural limitation to coronary flow in the hypertrophied myocardium. The finding of similar total coronary flow, but reduced flow per unit mass during maximal vasodilation, suggests that overall capacity of flow, but reduced flow per unit mass during maximal myocardium. The finding of similar total coronary flow and myocardial function become impaired in the hypertrophied heart despite increased myocyte size.54-56

In conclusion, although the hypertrophy process can limit increases in systolic wall stress in the presence of chronically increased left ventricular afterload, this beneficial effect is offset by the apparent mismatch of coronary vascular capacity and myocardial mass in the hypertrophied heart. Physiological coronary flow reserve is thus reduced, resulting in a shift of the lower limits of autoregulation to higher coronary perfusion pressures. When coronary perfusion pressure is reduced, coronary flow and myocardial function become impaired in the hypertrophied ventricle at pressures that do not adversely affect the normal ventricle. Like the normal heart, the hypertrophied heart possesses an additional pharmacological flow reserve, but appears unable to recruit this reserve to restore autoregulatory capacity at low perfusion pressures.

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