Effect of Tachycardia on Regional Function and Transmural Myocardial Perfusion During Graded Coronary Pressure Reduction in Conscious Dogs

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The purpose of the present study was to examine subendocardial flow and function during graded coronary pressure reduction to determine the effect of tachycardia on the lower autoregulatory pressure limit (critical coronary pressure) in unanesthetized dogs. During atrial pacing at a rate of 200 beats/min, subendocardial flow measured by radioactive microspheres averaged \(1.55 \pm 0.34\) ml/min/g and remained unchanged as pressure was reduced over the autoregulatory plateau from \(84 \pm 10\) to \(59 \pm 7\) mm Hg. Further reductions in coronary pressure to below a critical coronary pressure of \(~60\) mm Hg were associated with concomitant reductions in subendocardial flow and the endocardial-epicardial flow ratio during tachycardia. Although regional function remained constant over the autoregulatory plateau, there was a rightward shift of the coronary pressure-function relation during ischemia in response to a steady-state increase in rate from 100 to 200 beats/min. Reductions in regional wall thickening began when coronary pressures reached \(38 \pm 7\) mm Hg at a heart rate of 100 beats/min and \(61 \pm 6\) mm Hg at a heart rate of 200 beats/min \((p<0.005)\). Similar critical coronary pressure values were obtained for subendocardial segment shortening. Relations between subendocardial flow and myocardial function measured by both transmural wall thickening and subendocardial segment shortening were linear during pacing at a heart rate of 200 beats/min with relative reductions in wall thickening related to reductions in subendocardial flow on a nearly one-to-one basis. The results of this study demonstrate that there is a shift in the lower limit of subendocardial autoregulation during tachycardia as manifest by the onset of subendocardial ischemia at a higher distal coronary artery pressure. The shift in critical coronary pressure relates to an increase in resting flow requirements due to increased demand and diminished subendocardial vasodilator reserve at any given coronary pressure secondary to a reduction in the time available for diastolic subendocardial perfusion during tachycardia. \(\textit{Circulation} 1990;82:1815-1825\)

The physiological significance of a given coronary artery stenosis represents a complex interaction between the pressure-flow characteristics of the stenosis along with the adequacy of autoregulatory adjustments to maintain subendocardial perfusion as demand is increased.\(^1,2\) When pressure distal to a stenosis falls to a critical level, autoregulatory mechanisms are no longer able to maintain the prevailing level of flow and oxygen delivery, which results in myocardial ischemia. This is initially manifest in the inner myocardial layers by concomitant reductions in subendocardial perfusion and function.\(^3-5\) Studies in anesthetized animals have demonstrated subendocardial ischemia to begin when distal coronary pressure falls to less than 70 mm Hg.\(^6,7\) In contrast, recent studies in conscious animals from our laboratory have demonstrated subendocardial flow and function to remain normal until distal coronary pressure decreases to less than 40 mm Hg.\(^5\) The considerable difference in the lower autoregulatory pressure limit (critical coronary press-
sure) between these studies is difficult to explain on the basis of differences in either resting flow levels or compressive effects related to heart rate between awake and anesthetized animals. Although the effect of tachycardia on transmural perfusion has been studied in models of fixed coronary stenosis as well as during pharmacological vasodilation at normal coronary pressures, little is known regarding the effect of tachycardia on transmural autoregulatory responses of the distal vascular bed. Furthermore, how tachycardia influences the critical coronary pressure remains undefined.

We performed the present study to determine the effect of an increase in heart rate from 100 to 200 beats/min on transmural autoregulation in chronically instrumented unanesthetized dogs. Previously, we demonstrated that the relation between coronary pressure and subendocardial function can be used to define the critical coronary pressure for subendocardial autoregulation in a fashion similar to microsphere flow measurements. The specific goals of this study were to use microsphere measurements of transmural perfusion to determine the shift in the critical coronary pressure after a steady-state increase in heart rate to 200 beats/min and to determine whether the relation between coronary pressure and regional function could be used to characterize the critical coronary pressure in the face of substantial changes in baseline wall thickening and segment shortening after an increase in heart rate from 100 to 200 beats/min.

**Methods**

Studies were conducted in chronically instrumented dogs. All experimental procedures were performed in accordance with institutional guidelines. A total of 16 mongrel dogs [27±3 (±SD) kg] were studied.

**Experimental Preparation**

The details of the experimental preparation may be found elsewhere. Briefly, we induced anesthesia by intravenous injection of sodium thiopental (20 mg · kg$^{-1}$ i.v.). After endotracheal intubation, a surgical plane of anesthesia was maintained with a nitrous oxide (−60%), oxygen (−40%), and halothane (−1−2%) mixture. We then performed a thoracotomy in the fifth left intercostal space using aseptic technique. Tygon catheters were inserted into the left atrium and descending aorta for microsphere injection and reference blood flow withdrawal. Pacing leads were sewn onto the left atrial appendage. A Konigsberg micromanometer (P6.5) was inserted into the left ventricular apex. We dissected a 1−2-cm length of the left circumflex artery free and placed a hydraulic occluder around it, proximal to the first marginal branch. Teflon angiocaths were inserted into the distal circumflex artery as well as into the ascending aorta for pressure measurement. Regional myocardial function in the distal circumflex as well as in the anterior descending free wall was measured using ultrasonic crystal pairs placed to measure both subendocardial segment shortening and transmural wall thickening. Crystals were placed as previously described and excluded from data analysis if they were not in the inner quarter of the myocardial wall (wall thickness, $n=1$; segment length, $n=3$). At the conclusion of instrumentation, the chest was closed, the catheters and wires were exteriorized, and the pneumothorax was evacuated. We administered streptomycin (300 mg i.m.) and procaine penicillin (300,000 units i.m.) for 3−5 days postoperatively. Enteric-coated aspirin (325 mg p.o. q.d.) was begun on the fourth postoperative day. Catheters were flushed and filled with heparin as previously described. The animals were allowed to recover for at least 10 days before the experimental protocols were begun.

**Coronary Pressure-Function Relations**

Relations between steady-state reductions in coronary pressure and circumflex function were determined during tachycardia in 15 animals. In eight of the animals, coronary pressure-function relations were analyzed at the spontaneous heart rate (−100 beats/min) as well as during atrial pacing at a rate of 200 beats/min. Because we have previously found regional function to be reversibly depressed upon restoring coronary pressure after graded pressure reduction, we performed studies at each heart rate on separate days in a random fashion. Rate-related atrioventricular block frequently developed during atrial pacing at the higher heart rate. To circumvent this and maintain atrioventricular synchrony, atropine (0.5−1.0 mg i.v.) was given and supplemented with additional doses if necessary. Most animals were studied during light sedation with Innovar-Vet (fentanyl 0.4 mg · ml$^{-1}$ and droperidol 20 mg · ml$^{-1}$, 1−3 ml i.m.). Although lightly sedated, the animals were conscious and exhibited stable hemodynamics for periods of 2−3 hours.

Measurements of hemodynamics and regional function were obtained while the animals were lying quietly on their right sides. Pressure transducers (Statham P23dB) were referenced to the dorsal spine, and the micromanometer was calibrated in vivo by matching peak systolic pressure to systolic aortic pressure and end-diastolic pressure to the atrial wave of the left atrial pressure tracing. After allowing 30 minutes for the animal to adjust to the laboratory, we produced steady-state reductions in distal circumflex pressure by progressively inflating the hydraulic occluder to produce stenoses of increasing severity. We waited at least 60 seconds between measurements and allowed longer intervals if function and/or distal pressure had not yet equilibrated. Coronary pressure was reduced in 2−5−mm Hg increments until circumflex function began to fall after which smaller reductions in pressure were used. Once function began to fall, coronary pressure and function were not allowed to return to control until the end of each study.

We have previously documented that regional function usually remains unchanged at coronary press-
sures of more than 40 mm Hg at heart rates of 100 beats/min. At rates of 200 beats/min in the present study, circumflex wall thickening and segment shortening usually remained constant until coronary pressure reached 60 mm Hg. Thus, to determine control values of function as well as its variability under nonischemic conditions, we averaged hemodynamic data at coronary pressures above 70 mm Hg at a rate of 200 beats/min and 50 mm Hg at a rate of 100 beats/min. All individual measurements of function were then expressed as a percent of the mean control values in the same fashion that we have previously described. The variability in function and systemic hemodynamics throughout individual experiments was expressed using the coefficient of variation.

Coronary pressure-function relations were constructed using measurements of pressure and circumflex wall thickening or segment shortening that were associated with subendocardial ischemia. We have previously described the details of this elsewhere. Briefly, each relation was fit using linear regression of all pressure-function points where function was less than 90% of the mean control value. Critical pressures were determined by extrapolating these relations to the coronary pressure corresponding to 100% of the control value of function. Coronary pressures corresponding to selected levels of function reduction were also calculated from the individual regression relations. To avoid bias related to the extrapolation of pressure-function relations outside of the data range, we excluded experiments in which function remained at more than 50% of control values during the most severe occlusion. Although function fell to less than 50% of control values in all animals during tachycardia, it remained above this in seven animals at the lower heart rate. Therefore, we compared the effect of tachycardia on the pressure-function relation using the eight animals in which an appropriate range of data was available for segment shortening and/or wall thickening at each rate. During tachycardia, reductions in function were correlated with mean coronary pressure, mean diastolic coronary pressure, and end-diastolic coronary pressure. The slope and intercept as well as the coronary pressures corresponding to selected levels of functional reduction were tabulated.

**Transmural Coronary Autoregulation**

Transmural variations in autoregulation were examined in 13 of the animals during atrial pacing at a rate of 200 beats/min. We measured regional myocardial perfusion with radionuclide-labeled microspheres using the reference withdrawal technique. Animals were anticoagulated during each experiment (sodium heparin, 5,000 units i.v.). As many as seven flow measurements were performed in individual animals using 15-μm-diameter microspheres labeled with the following gamma-emitting nuclides: 152Gd, 57Co, 113Sn, 115In, 90Nb (New England Nuclear, Boston), 51Cr, 85Sr, and 46Sc (3M Incorporated, St. Paul, Minn.). Microspheres were placed in an ultrasonica-tor for at least 15 minutes and vortex agitated before injection. We injected 2–4×1010 microspheres into the left atrium during a 10–15-second period and flushed the catheter with warm arterial blood. A reference withdrawal sample was begun from the descending aorta (5 ml · min⁻¹) before microsphere injection and continued for 2 minutes to quantify regional myocardial perfusion. We measured flow during atrial pacing at the spontaneous coronary pressure in each of the animals. In six animals, we repeated flow measurements when coronary pressure was reduced by 20–30 mm Hg in the presence of maintained endocardial function (nonischemic). The remainder of the flow measurements were performed during reductions in pressure that resulted in measureable reductions of regional myocardial function. Systemic and coronary hemodynamics were monitored throughout the withdrawal period, and flow measurements were excluded from further analysis if there were abrupt changes in hemodynamics. This resulted in the exclusion of eight of 61 flow measurements.

At the conclusion of each experiment, the animals were killed with potassium chloride overdose during deep barbiturate anesthesia. The hearts were removed and placed in formalin for several days. The left ventricle was sliced into four concentric rings, and the apex was discarded. Each ring was divided into eight wedges with the anterior and posterior papillary muscles counted separately. Each sample was weighed, and the activity was determined using a sodium iodide detector (Tracor-Northern). The activity of individual isotopes was determined using a least-squares radionuclide separation technique. Myocardial perfusion was calculated from the activity measurements as previously described. Wedges in the circumflex region containing the ultrasonic crystals represented the ischemic core. Flow in samples surrounding the core region were analyzed to exclude the possibility that they may have represented an admixture of normal and ischemic myocardium. Control nonischemic zone flow was assessed in the anterior descending free wall for each isotope. We determined the relative circumflex flow reduction by expressing myocardial flow in each transmural layer of the circumflex core as a ratio of the corresponding values in the nonischemic anterior descending zone. Flows during coronary pressure reduction were then normalized to the control flow ratio obtained at a normal pressure and expressed as a percent. This type of normalization scheme has been used by researchers at our laboratory as well as at others to control for both spatial and temporal heterogeneity in myocardial perfusion. Using this scheme, we grouped circumflex subendocardial flow measurements with depressed circumflex function as nonischemic or more than 90% of control, 67–90% of control, 34–66% of control, and 33% or less of control. When multiple measurements for a given animal fell within the same group, the flows and hemodynamic parameters were averaged to obtain one value and thus avoid biasing the tabulated results.
In one animal, the left circumflex pressure catheter was not operational at the time of study, and only myocardial flow-function relations were determined.

**Data Analysis**

Experimental data were recorded on an eight-channel Gould 2800 W recorder at a paper speed of 100 mm \cdot \text{sec}^{-1}. All data were digitized at a sampling rate of 200 Hz using a Data Translation DT 2801-A analog-to-digital converter interfaced to an IBM PC AT computer. All data represent averages of a 15-second sampling interval comprising at least 20 cardiac cycles.

Signals from the ultrasonic crystals were processed using a Triton Technology (San Diego, Calif.) sonomicrometer. Left ventricular pressure was differentiated with a filter cutoff of 100 Hz. The first derivative of left ventricular pressure (dP/dt) was used to determine end diastole (ED; onset of positive dP/dt) and end systole (ES; 20 msec before peak negative dP/dt). From these measurements, the systolic excursion for wall thickness (Δ WT) and segment length (Δ SL) were calculated as follows: Δ WT=ESWT−EDWT and ΔSL=EDSL−ESSL. Percent wall thickening and percent segment shortening were determined as follows: \%WT=ΔWT/EDWT and \%SS=ΔSL/EDSL.

Constancy of systemic hemodynamics throughout each study was determined by measuring heart rate, mean aortic pressure, systolic and end-diastolic left ventricular pressures, peak positive dP/dt, and peak negative dP/dt. Several indexes of coronary driving pressure were calculated from the digitized data. Mean coronary pressure was averaged over the entire cardiac cycle. End-diastolic coronary pressure was taken at the onset of positive dP/dt. To calculate mean diastolic coronary pressure, diastole was defined as occurring between the point where left ventricular pressure fell below coronary pressure until it exceeded it again during systole for each cardiac cycle. Coronary pressure during this period was then averaged. We calculated closed-loop autoregulatory gain \( G_z \) to assess steady-state flow regulation over the autoregulatory plateau as previously described.\(^\text{12} \)

**Statistics**

All values are given as mean±1 SD unless otherwise indicated. Data for microsphere flow measurements were analyzed with a one-way analysis of variance. Significant differences between each level of stenosis and the corresponding control values were determined using a two-tailed paired \( t \) test. A \( p \) value of less than 0.05 was considered significant.

Regression analyses of pressure-function relations were performed using a least-squares linear fit. Flow-function relations were determined using linear fits as well as second-order polynomials.\(^\text{13} \)

**Results**

Hemodynamic changes in response to atrial pacing under nonischemic conditions at the spontaneous distal circumflex pressure are illustrated for a representative experiment in Figure 1. Heart rate increased from 108±22 (mean±SD, \( n=8 \)) to 203±3 beats/min during pacing. After the twofold increase in rate, left ventricular end-diastolic pressure decreased (5.5±4.1 to 2.3±2.8 mm Hg, \( p<0.05 \)), and systolic aortic pressure increased significantly (108±9 to 115±9 mm Hg, \( p<0.05 \)). There was an increase in end-diastolic wall thickness from 9.9±0.8 to 10.7±0.9 mm (\( p<0.01 \)) and a reduction in end-diastolic segment length from 15.1±2.8 to 13.7±2.4 mm (\( p<0.01 \)), both reflecting a reduction in left ventricular end-diastolic volume. Ejection phase indexes of regional circumflex function decreased significantly during pacing at normal coronary pressures and in the absence of ischemia. Wall thickening decreased from 23.5±8.4% to 16.7±3.8% (\( p<0.05 \)), and segment shortening decreased from 17.9±5.1% to 11.1±5.4% (\( p<0.01 \)). Similar changes were observed in the anterior descending region. Arterial blood gases at the time of study for all animals were as follows: pH 7.42±0.03; PCO\(_2\), 33±3 mm Hg; and PO\(_2\), 73±7 mm Hg. Hematocrit averaged 35±5%.

**Effect of Tachycardia on Coronary Pressure-Function Relation**

The effect of tachycardia on coronary pressure-function relations for an individual animal is illustrated in Figure 2. Despite substantial reductions in percent wall thickening and percent segment shortening during pacing (upper panels), the prevailing level of function remained constant as stenosis severity was increased until mean coronary pressure reached approximately 53 mm Hg at a rate of 200 beats/min. At a rate of 100 beats/min, function remained constant until coronary pressure decreased to 37 mm Hg. Below these critical pressures, further reductions in coronary pressure resulted in pronounced reductions in absolute wall thickening and segment shortening that were linearly related to mean coronary pressure. When expressed as a percent of the prevailing control function at each heart rate (normalized wall thickening and segment shortening, lower panels), there was a shift to the right of the coronary pressure-function relation during tachycardia. Because of this shift, similar relative reductions in function occurred at higher distal coronary pressures during tachycardia. Coronary pressures corresponding to selected reduced levels of circumflex function are summarized for the eight animals studied at each of the two heart rates (Figure 3). When pressure-function relations at 100 beats/min were compared with those at 200 beats/min, the critical pressure at which wall thickening began to fall increased from 38±7 to 61±6 mm Hg (\( p<0.005 \), \( n=6 \)), and the critical pressure at which segment shortening began to fall increased from 39±7 to 64±3 mm Hg (\( p<0.001 \), \( n=7 \)).

Pressure-function relations performed during tachycardia at a rate of 200 beats/min for all animals studied are summarized in Table 1. Systemic hemodynamics
remained essentially constant as coronary pressure was varied over the autoregulatory plateau. Function in the circumflex region remained unchanged (coefficient of variation, approximately ±5% of the mean) as coronary pressure was varied at pressures above the critical coronary pressure. Wall thickening began to decrease at a slightly lower mean coronary pressure than segment shortening (59.9±6.1 versus 62.1±6.6 mm Hg), but this difference was not statistically significant. Critical pressures obtained using diastolic coronary pressure indexes were lower than those for mean full-cycle coronary pressure (Table 1). Wall thickening began to decrease when mean diastolic coronary pressure reached 49.6±8.4 mm Hg and end-diastolic coronary pressure reached 38±9.7 mm Hg. Corresponding values for segment shortening were 51.2±5.9 and 39±5.8 mm Hg.

Transmural Variations in Autoregulation During Tachycardia

Under control conditions at a heart rate of 200 beats/min, subendocardial flow for all animals aver-
aged 1.55±0.34 ml · min · g⁻¹, subepicardial flow was 1.41±0.47 ml · min⁻¹ · g⁻¹, and the endocardial-epicardial (endo/epi) flow ratio averaged 1.14±0.18. Regional myocardial flow, function, and distal coronary pressure at selected levels of subendocardial flow reduction are summarized in Table 2. When coronary pressure was reduced over the autoregulatory plateau from 84 to 59 mm Hg, there was a 2% reduction in subendocardial flow (Gc, 0.93) and a 9% decrease in subepicardial flow (Gc, 0.70), neither of which was significant from control. Below a mean pressure of approximately 60 mm Hg, further reductions in coronary pressure were associated with significant reductions in subendocardial flow and function as well as in the endo/epi flow ratio (Table 2). In contrast to the reductions in subendocardial flow, subepicardial flow did not change significantly despite mean coronary pressure decreasing to as low as 33±5 mm Hg.

Critical pressures for subendocardial autoregulation using diastolic indexes of coronary driving pressure were considerably lower than those for mean coronary pressure (Table 2). Subendocardial flow remained constant until mean diastolic coronary pressure reached 49±8 mm Hg and end-diastolic pressure reached 37±7 mm Hg. Of particular importance was the finding that the critical pressures based on the steady-state autoregulatory pressure-flow relation were similar to those determined using coronary pressure-function relations (coronary pressure values corresponding to 100% function in Table 1).

Flow-Function Relations During Tachycardia

Under ischemic conditions, relative reductions in subendocardial flow during tachycardia were closely coupled to relative reductions in both transmural wall thickening and subendocardial segment shortening (Table 2). The flow-function relation between subendocardial flow and wall thickening during mild-to-moderate ischemia was nearly one-to-one. The relation between wall thickening reductions (y) and subendocardial flow (x) as a percent of control could be described by the following linear relation: y=0.88x+8.4 (n=53, r=0.84). The quadratic relation was essentially the same: y=−0.004x²+0.88x+8.2 (n=53, r=0.84). The magnitude of segment shortening reduction tended to exceed the relative reduction in subendocardial flow but could also be described by a linear relation that was steeper than that for wall thickening: y=2.25x−137.0 (n=48, r=0.83). Both wall thickening and segment shortening reductions were dissociated from subepicardial flow, which
remained unchanged in the face of severe subendocardial ischemia (Table 2).

**Discussion**

The major finding of this study is that there is a shift in the critical pressure for subendocardial autoregulation from approximately 40 to 60 mm Hg in response to a twofold increase in heart rate in conscious dogs. Although changes in ejection-phase indexes of regional function occurred during tachycardia, transmural wall thickening and subendocardial segment shortening remained constant over the autoregulatory plateau, and the coronary pressure-function relation during myocardial ischemia continued to be linear. Furthermore, despite an increase in resting flow and a reduction in absolute wall thickening during tachycardia, relative reductions in wall thickening continued to be related to relative reductions in subendocardial flow on a nearly one-to-one basis during steady-state ischemia.

**Effect of Tachycardia on Transmural Autoregulation**

We found subendocardial flow to be autoregulated to meet resting metabolic needs (as assessed by maintained regional function) over a narrower pressure range as heart rate increased from 100 to 200 beats/min. This resulted in the onset of subendocardial ischemia at higher critical coronary pressures at a rate of 200 beats/min in comparison to a previous study from our laboratory in unanesthetized dogs at a rate of 100 beats/min. The subendocardial autoregulatory relation from the present study at a heart rate of 200 beats/min is compared with that from this previous study (Figure 4). Although resting flow increased by approximately 50% after a twofold increase in heart rate, there was little change (less

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Plots of comparison of coronary pressure-function relations from animals studied at each of the two heart rates (HRs). •, 200 beats/min; △, 100 beats/min. Mean coronary pressure at selected levels of regional function reduction are summarized for wall thickening (upper panel) and segment shortening (lower panel). Function remained constant until mean coronary pressure decreased to ~40 mm Hg at a rate of 100 beats/min compared with ~60 mm Hg when HR was increased to 200 beats/min. Values are given as mean±1 SEM.

**Table 1.** Pressure-Function Experiments at Heart Rate of 200 Beats/Min: Coronary Pressure-Function Relations

<table>
<thead>
<tr>
<th>Abscissa parameter</th>
<th>Normalized LC WT (n=14)</th>
<th>100%</th>
<th>50%</th>
<th>0%</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC pressure (mm Hg)</td>
<td>Mean</td>
<td>59.9±6.1</td>
<td>45.9±4.5</td>
<td>31.8±5.0</td>
<td>3.86±1.10</td>
<td>-126±48</td>
<td>0.93±0.05</td>
</tr>
<tr>
<td></td>
<td>Mean diastolic</td>
<td>49.6±8.4</td>
<td>35.9±5.4</td>
<td>22.3±5.3</td>
<td>4.16±1.46</td>
<td>-96±48</td>
<td>0.93±0.04</td>
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<tr>
<td></td>
<td>End diastolic</td>
<td>38.0±9.7</td>
<td>27.0±5.2</td>
<td>15.9±4.0</td>
<td>5.72±2.68</td>
<td>-96±61</td>
<td>0.90±0.06</td>
</tr>
<tr>
<td>Normalized LC SS (n=12)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Abscissa parameter</td>
<td>Mean</td>
<td>0%</td>
<td></td>
<td>Slope</td>
<td>Intercept</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td>LC pressure (mm Hg)</td>
<td>62.1±6.6</td>
<td>53.5±6.6*</td>
<td>44.9±8.0*</td>
<td>6.96±3.21†</td>
<td>-329±211*</td>
<td>0.94±0.06</td>
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<tr>
<td></td>
<td>Mean diastolic</td>
<td>51.2±5.9</td>
<td>42.9±6.1†</td>
<td>34.6±7.5*</td>
<td>7.15±2.80*</td>
<td>-260±152*</td>
<td>0.94±0.05</td>
</tr>
<tr>
<td></td>
<td>End diastolic</td>
<td>39.0±5.8</td>
<td>32.5±5.4†</td>
<td>26.1±6.0*</td>
<td>9.41±3.54†</td>
<td>-253±137*</td>
<td>0.93±0.06</td>
</tr>
</tbody>
</table>

100%, 50%, and 0% indicate values of coronary pressure (mm Hg) that correspond to three selected levels of regional function reduction for normalized wall thickening (LC WT) and normalized segment shortening (LC SS). 100% indicates the critical pressure for each index of coronary driving pressure. Slope and intercept represent the mean linear coefficients from the pressure-function relation for each abscissa parameter, and r is the linear correlation coefficient.

Values are given as mean±1 SD.

* *p<0.005 versus corresponding wall thickening values.
† *p<0.05 versus corresponding wall thickening values.
Table 2. Transmural Coronary Flow, Function, and Distal Coronary Pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>Normalized LC/LAD endocardial flow (% control endocardial flow)</th>
<th>( P_{\text{LC}} ) (mean ± SD)</th>
<th>( P_{\text{LC}} ) (mean ± SD)</th>
<th>( P_{\text{LC}} ) (mean ± SD)</th>
<th>LC flow (ml·min⁻¹·g⁻¹)</th>
<th>LC WT (%)</th>
<th>LC SS (%)</th>
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</thead>
<tbody>
<tr>
<td>Nonischemic</td>
<td></td>
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<td>( n=6 )</td>
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<td>C</td>
<td>6</td>
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<td>6</td>
</tr>
<tr>
<td>S</td>
<td>1.01±0.07</td>
<td>59±7</td>
<td>37±7</td>
<td>49±8</td>
<td>1.38±0.42</td>
<td>1.22±0.51</td>
<td>1.16±0.17</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>67-90% ( n=8 )</td>
<td></td>
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<tr>
<td>C</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
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<td>8</td>
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<tr>
<td>S</td>
<td>0.81±0.08</td>
<td>52±5</td>
<td>29±3</td>
<td>40±5</td>
<td>1.17±0.31</td>
<td>1.27±0.37</td>
<td>0.94±0.20</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
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<tr>
<td>34-66% ( n=7 )</td>
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<tr>
<td>C</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>S</td>
<td>0.50±0.08</td>
<td>42±6</td>
<td>22±3</td>
<td>32±4</td>
<td>0.77±0.23</td>
<td>1.43±0.47</td>
<td>0.55±0.09</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
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<tr>
<td>≤33% ( n=5 )</td>
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<td>S</td>
<td>0.25±0.06</td>
<td>33±5</td>
<td>19±2</td>
<td>24±3</td>
<td>0.43±0.19</td>
<td>1.33±0.46</td>
<td>0.32±0.07</td>
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<td>P</td>
<td>&lt;0.001</td>
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\( n \), measurements in each group; C, control; S, stenosis; P, statistical significance for two-tailed paired \( t \) test. Values are given as mean±1 SD.

Measurements have been grouped into four levels of pressure and flow reduction as described in the text. Normalized LC/LAD endocardial flow, normalized left circumflex/left anterior descending coronary subendocardial flow ratio for total perfused region calculated as described in the text; LC, circumflex region; LAD, left anterior descending region; \( P_{\text{LC}} \), left circumflex pressure; WT, wall thickening; SS, segment shortening.

FIGURE 4. Plots of endocardial flow measurements during autoregulation from the present study at a heart rate (HR) of 200 beats/min (■) compared with those previously reported from our laboratory at a rate of 100 beats/min (△). When rate was increased from 100 to 200 beats/min, coronary flow at any given pressure during ischemia decreased consistent with a reduction in endocardial vasodilator reserve. This, along with an ~50% increase in resting flow requirements, caused the critical pressure for subendocardial autoregulation to increase from 40 to 60 mm Hg during tachycardia.

than 10%) in the prevailing level of subendocardial or subepicardial flow as coronary pressure was reduced over the autoregulatory plateau at either heart rate. Harrison et al. also found no significant change in flow over the autoregulatory plateau (coronary pressures, >75 mm Hg) in conscious animals with as well as without left ventricular hypertrophy. The constancy of flow indicates that there is little reliance on enhanced oxygen extraction to maintain oxygen delivery as coronary artery pressure is reduced over the autoregulatory plateau in conscious animals. This contrasts with studies in anesthetized animals that report reductions in coronary flow occur over the autoregulatory plateau in association with significantly increased oxygen extraction and maintained regional function. When we compared the degree of autoregulation at each heart rate by calculating the closed-loop autoregulatory gain \( (G_c) \), subendocardial \( G_c \) increased from 0.87 to 0.93, whereas epicardial \( G_c \) decreased from 0.80 to 0.70 after an increase in rate. These small differences argue against a systematic effect of increased metabolic demand on the characteristics of steady-state autoregulation above the critical pressure in our preparation. This conclusion contrasts with that reached by Dole and Nunn which anesthetized dogs; they found that \( G_c \) increased from ~0.15 to 0.33 as metabolic demand was increased by pacing from 40 to 120 beats/min.

The effect of tachycardia on the critical pressure in conscious dogs has not previously been determined. The critical pressure occurred at 60 mm Hg in the present study compared with 40 mm Hg in a prior study from our laboratory at a rate of 100 beats/min. At least part of this difference is related to pacing-induced changes in resting subendocardial flow (1.06 versus 1.55 ml·min⁻¹·g⁻¹), which are similar to
differences previously found by others. In addition to the increase in resting flow, we found subendocardial flow during ischemia to be lower during tachycardia when levels of coronary pressure below 40 mm Hg were compared at each rate (Figure 4). This finding was presumably a manifestation of the effect of time-averaged compressive forces on subendocardial vasodilator reserve, which have previously been demonstrated during pharmacological vasodilation at normal coronary pressures. Thus, vulnerability of the subendocardium to demand-induced ischemia is the result of a shift in the critical pressure of autoregulation. As heart rate rises, this critical pressure increases because of a reduction in subendocardial vasodilator reserve as well as an increase in resting subendocardial flow required to meet increased myocardial metabolic needs during tachycardia. Additional factors such as time-dependent diastolic reopening of subendocardial vessels closed during systole could also be operative.

Two studies have examined transmural variations in autoregulation at reduced pressures in open-chest anesthetized dogs. Both demonstrated significantly higher critical pressures at the onset of ischemia in comparison to results in unanesthetized dogs in the present as well as our previous study. In comparing the critical pressure among different studies, potential differences may relate to variability in metabolic demand and vasodilator reserve related to heart rate, afterload, and contractility. In these two previous studies in anesthetized animals, heart rates were lower than those encountered in the present study. Thus, the effects of heart rate on resting flow requirements (i.e., demand) and subendocardial vasodilator reserve were presumably less than those in our study. Despite this, critical pressures were equal to or higher than those in the present study. Guyton et al reported subendocardial flow to decrease when mean coronary pressure fell to less than 70 mm Hg at a heart rate of 150 beats/min compared with a pressure of 60 mm Hg at a rate of 200 beats/min in the present study. Although the precise critical pressure was not quantified in the study of Rouleau et al, mean flow began to fall when mean diastolic coronary pressure reached 50 mm Hg (Figure 1, Reference 7). This critical pressure is similar to the present study in which heart rate and resting flow were higher. A recent study by Jeremy et al in anesthetized dogs reported that subendocardial segment shortening and coronary flow began falling when end-diastolic coronary pressure fell to less than 53 mm Hg at a heart rate of 130 beats/min, which is also greater than the end-diastolic value of 37 mm Hg at a rate of 200 beats/min in the present study. Thus, our results, which demonstrate lower critical pressures at even higher levels of heart rate and resting flow than those in these anesthetized studies, support the notion that differences in the critical pressure for subendocardial autoregulation between awake and anesthetized animals are probably secondary to other factors. Factors could include acute surgical instrumentation or elevated circulating catecholamine levels, which may act to modulate coronary autoregulatory responses in the acute experimental setting. In addition to these factors, a study comparing autoregulation in the same preparation before and after various inhaled anesthetics by Hickey et al indicates that anesthetic agents may affect coronary autoregulatory responses in some experimental preparations.

Coronary Pressure-Function and Subendocardial Flow-Function Relations During Tachycardia

Despite load-dependent changes in baseline function after an increase in rate from 100 to 200 beats/min, we found the prevailing level of regional function to remain constant as coronary pressure was initially reduced over the autoregulatory plateau. Previous studies examining coronary autoregulation in anesthetized animals have sometimes demonstrated a "Gregg effect," or reductions in flow and myocardial oxygen consumption as coronary artery pressure is reduced over the autoregulatory plateau. The results of the present study indicate that there is no major change in subendocardial flow or function over the autoregulatory plateau when rate is increased to 200 beats/min in this experimen-
tal preparation and is similar to our previous study at a rate of 100 beats/min. Although we could not measure subendocardial oxygen consumption, the failure of subendocardial oxygen delivery and function to change as coronary pressure is varied above the critical pressure argues against a major change in oxygen consumption and indicates that the Gregg phenomenon may not be of major importance in conscious animals.

Below the critical pressure, relative reductions in function at constant levels of global demand continued to be linearly related to reductions in coronary pressure. At a rate of 200 beats/min, segment shortening reductions began when mean coronary pressure decreased to ~62 mm Hg, and wall thickening reductions began when mean coronary pressure decreased to ~60 mm Hg. The lack of a difference in the critical pressure between the two measurements of regional function indicates that each provides an equally sensitive index of the onset of subendocardial ischemia. When regional function was related to diastolic indexes of coronary driving pressure compared with mean full-cycle coronary pressure, the onset of myocardial ischemia occurred at lower critical pressures.

Previous studies from other laboratories as well as from our own have demonstrated a close coupling between relative reductions in regional function and subendocardial flow in conscious dogs during myocardial ischemia when global demand is kept constant and stenosis severity is increased in steady-state increments. The results from the present study indicate a continued close coupling between subendocardial flow and function during ischemia after a steady-state increase in demand produced by atrial pacing. Our findings also agree with those of these previous studies at resting heart rates in demonstrating a dissociation between subepicardial flow and both transmural wall thickening and subendocardial segment shortening during graded ischemia.

Despite a significant increase in resting subendocardial flow and load-dependent reductions in absolute wall thickening when heart rate was increased to 200 beats/min, we continued to find reductions in wall thickening to be related to reductions in subendocardial flow on a nearly one-to-one basis during mild-to-moderate subendocardial ischemia. This relation was similar to that we had found during graded pressure reduction at a rate of 100 beats/min. This similarity suggests that despite absolute changes in resting flow and load-dependent changes in function during atrial pacing, relative reductions in wall thickening at any given heart rate can provide an indirect assessment of the relative degree to which subendocardial flow decreases as coronary pressure is reduced to below the lower autoregulatory pressure limit. In contrast, although reductions in segment shortening were also linearly related to subendocardial flow, there was an increase in the slope of the relation compared with that we previously found at a rate of 100 beats/min. Because of this, akinesis of segment shortening occurred when subendocardial flow was reduced to only 61% of control at a rate of 200 beats/min compared with 30% of control at a rate of 100 beats/min. Thus, although reductions in subendocardial shortening signal the onset of subendocardial ischemia during graded reductions in coronary pressure, the variability of the relation between segment shortening and subendocardial flow with heart rate seems to limit its use as a quantitative index of the relative magnitude of subendocardial flow reduction.

Clinical Implications

Based on the results of the present study, the effect of tachycardia on transmural perfusion during autoregulation may be placed in the context of a fixed epicardial coronary stenosis. Figure 5 schematically illustrates the curvilinear relation between distal coronary pressure for three stenoses of increasing severity (50%, 70%, and 90% diameter reduction). For any fixed level of coronary stenosis, distal coronary pressure decreases in a nonlinear fashion as resting flow requirements increase. For severe stenoses (e.g., 90%), small increases in flow can be associated with a large reduction in distal coronary pressure. A stenosis will become physiologically significant if distal coronary pressure decreases to below the critical lower autoregulatory pressure limit associated with a given increase in demand (illustrated by the arrows at the knee of the two autoregulatory relations).

Our results demonstrate a change in the autoregulatory relation during tachycardia that increases the critical distal coronary pressure required to maintain adequate subendocardial perfusion. This change is the net result of two factors. First, the autoregulatory plateau shifts upward during tachycardia due to the increased resting flow requirements necessary to meet a modest increase in demand. Second, the pressure-flow relation during vasodilation (as reflected by the pressure-flow points during ischemia) shifts to the right secondary to a reduction in the time available for subendocardial perfusion. Although the increase in the critical pressure may cause a 90% stenosis to become apparent in terms of eliciting subendocardial ischemia during tachycardia, it may fail to demonstrate a more modest stenosis (e.g., 70%) despite the latter having a significant reduction in coronary flow reserve during pharmacological vasodilation. Interventions that increase the critical pressure to even higher pressures, such as exercise, would cause these less severe stenoses to become functionally significant. A corollary to this is that the physiological consequences of a severe coronary stenosis may be minimized by interventions that decrease the lower pressure limit of adequate autoregulation. The latter could be accomplished by reducing resting demand (i.e., resting flow requirements) as well as by decreasing heart rate and increasing the time available for subendocardial perfusion.
Finally, in light of the nearly one-to-one relation between reductions in subendocardial flow and wall thickening demonstrated in the present study, quantitative measurements of regional wall thickening appear to provide some promise as indirect measurements of subendocardial perfusion. In this regard, the magnitude of wall thickening impairment in an ischemic region compared with a normally perfused region during graded levels of myocardial stress may provide a noninvasive approach to assess the physiological effects of a coronary stenosis in a more quantitative fashion. Further studies will be necessary to address this possibility more definitively.

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References


Key Words: coronary pressure-function relation • coronary stenosis • myocardial flow-function relation • autoregulation
Effect of tachycardia on regional function and transmural myocardial perfusion during graded coronary pressure reduction in conscious dogs.

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