Coronary Pressure-Function and Steady-State Pressure-Flow Relations During Autoregulation in the Unanesthetized Dog

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The present study was intended to define the interrelation among endocardial flow, endocardial function, and coronary arterial pressure during spontaneous autoregulation in the left ventricle of chronically instrumented unanesthetized dogs. Steady-state sonomicrometric measurements of regional function and epicardial coronary artery pressure were used to determine the lower pressure limit of endocardial autoregulation while global indexes of myocardial demand remained constant. Transmural wall thickening in the circumflex bed remained unchanged (±5% of control values) until coronary pressure fell below 39 ± 5.6 (SD) mm Hg. Endocardial segment shortening was similarly constant until coronary pressure fell below 42 ± 7.4 mm Hg. There was no significant change in endocardial flow as coronary pressure was reduced over the autoregulatory plateau from 84 to 49 mm Hg (1.05-0.99 ml/min/g, p = NS). Below the critical pressure limits, small additional reductions in pressure were associated with marked reductions in both endocardial flow and function. The coronary pressure-function relation was linear as well as steep across this range for both wall thickening (r = 0.94 ± 0.05) and segment shortening (r = 0.96 ± 0.03). Although the relation between endocardial flow and function showed more variability than pressure-function relations at low pressures, wall thickening reductions and endocardial flow reductions related on a nearly one-to-one basis. The present study establishes that the coronary pressure-function relation can be used to define the lower limit of endocardial autoregulation. It also indicates that the lower pressure limit of endocardial autoregulation is considerably less than in anesthetized animals (40 vs. 70 mm Hg) and that steady-state flow above this limit is controlled more tightly. Although these differences may relate to systemic hemodynamics, it seems likely that general anesthesia and/or acute surgical instrumentation alter coronary autoregulation under at least some experimental circumstances. (Circulation Research 1988;63:821-836)
under all circumstances). It is now well established that reductions in flow (and in some studies, myocardial function) occur at reduced coronary artery pressure in the presence of considerable vasodilator reserve, which is recruitable pharmacologically.11-14 Other studies have demonstrated that regional oxygen consumption decreases continuously as coronary pressure is reduced despite constant hemodynamic determinants of oxygen consumption.3,15,16

The potential effects of these changes on endocardial flow or a sensitive index of endocardial function have not been evaluated. Each such observation raises the possibility that factors other than local vasodilator reserve modulate coronary autoregulation under at least some experimental circumstances. Because acute instrumentation and general anesthesia have been shown to alter the relation between endocardial flow and function,9,10 it seems plausible that differences in coronary autoregulatory responses could also occur in these two experimental settings.

The present study was performed to define interrelations among coronary pressure, transmural myocardial perfusion, and endocardial function in chronically instrumented unanesthetized dogs. Specific aims were to 1) determine whether the relation between coronary pressure and endocardial function can be used to define the lower endocardial autoregulatory pressure limit; 2) quantify steady-state endocardial autoregulation and the degree to which regional flow and function (an indirect index of changes in endocardial oxygen consumption) may change over the autoregulatory "plateau," and 3) compare the relative sensitivity at comparable levels of regional ischemia of endocardial flow-function relations based on segment shortening and transmural wall thickening. The findings contrast with previous studies in anesthetized animals indicating both a significantly lower endocardial autoregulatory pressure limit (~40 mm Hg) and maintained oxygen delivery and function until this lower autoregulatory limit is reached.

Materials and Methods

Animal Preparation

Studies were conducted in awake, chronically instrumented dogs. All experimental procedures were performed in accordance with institutional guidelines. A total of 22 adult mongrel dogs (27 ± 2.3 [SD] kg) were studied. Anesthesia was induced by injection of sodium thiamylal (20 mg/kg i.v.). After endotracheal intubation, a surgical plane of anesthesia was maintained with a nitrous oxide (~60%), oxygen (~40%), and halothane (~1-2%) mixture during mechanical ventilation. Under sterile conditions, a thoracotomy was performed in the fifth left intercostal space.

The preparation is illustrated in Figure 1. Tygon catheters (0.0625 in. i.d., 0.125 in. o.d., 24 in. long) were placed into the left atrium and descending thoracic aorta for microsphere injection and reference blood sampling, respectively. Ascending aortic pressure was measured with a Teflon angiocath (22 gauge) inserted through vessel wall and connected to Tygon microbore tubing (0.02 in. i.d., 0.06 in. o.d., 24 in. long). The frequency response of this system when connected to a Statham P23dB pressure transducer and flushed with degassed saline was flat to at least 15 Hz and therefore sufficient to measure phasic variations in pressure at the heart rates encountered. Left ventricular pressure was measured by a Konigsberg Model P6.5 micromanometer placed through a stab wound in the ventricular apex and secured with a purse-string suture. Pacing leads were sewn onto the left atrial appendage. The left circumflex artery was dissected free for 1-2 cm proximal to the first marginal branch. A fluid-filled hydraulic occluder was placed around the proximal circumflex artery. A Teflon angiocath was inserted into the circumflex artery distal to the occluder with the tip facing downstream for coronary arterial pressure measurement, with care taken to avoid entering any side branches.

Endocardial function was measured in the distal circumflex and anterior descending region with piezoelectric crystals placed to measure both wall thickness and segment length, as previously described.17 Circumflex crystals were placed in the posterobasal free wall (above the minor axis), and anterior descending crystals were placed in the apical free wall region (below the minor axis), with care taken to avoid crystal placement in the anterior or posterior papillary muscles. In the majority of animals, segment length crystals spanned the same region occupied by the endocardial wall thickness crystal and, thus, assessed endocardial function in a similar anatomic region. Segment length crystals were oriented parallel to the estimated endocardial fiber orientation. For the inner quarter of the heart, this

![Schematic diagram of experimental preparation](http://circres.ahajournals.org/)

**Figure 1.** Schematic diagram of experimental preparation. LC, left circumflex; LAD, left anterior descending coronary artery; \( P_{\text{LC}} \), left circumflex pressure; \( P_{\text{Ao}} \), aortic pressure; \( P_L \), left ventricular pressure; LA, left atrium. (See text for discussion.)
angle (α) varies significantly with respect to the circumferential plane (α = +10° to +50°, Figure 5, reference 18). Because of these endocardial variations in fiber orientation with depth, the segment length crystals were inserted at an approximate angle of +30° to the circumferential plane. The position of the crystals was carefully examined at the time of necropsy. Six segment length pairs and two wall thickness pairs were excluded because they were not appropriately positioned. The innermost edge of the endocardial wall thickness crystals spanned 92 ± 8% of the myocardium. Segment length pairs were located 90 ± 10% of the distance across the wall.

At the conclusion of instrumentation, the crystal wires and catheters were tunneled through individual stab wounds in the 6th–7th left intercostal space. The chest was closed, and the pneumothorax evacuated with a chest tube. Animals were given streptomycin (300 mg i.m.) and procaine penicillin (300,000 units i.m.) for 3–5 days after surgery. Catheters were flushed with sterile saline and filled with heparin at 1–3-day intervals (10,000 units/ml for the circumflex artery catheter and 1,000 units/ml for all other catheters). Enteric coated aspirin (325 mg p.o.) was begun on the fourth day after surgery and administered daily thereafter.

Transmural Coronary Autoregulation

Microsphere flow studies were conducted in 16 animals 19±11 days after instrumentation. Most studies were conducted during light sedation with Innovar-Vet (fentanyl 0.4 mg/ml and droperidol 20 mg/ml, 1–3 ml i.m.). The use of this sedation resulted in stable systemic hemodynamics for 2–3 hours with substantially less variability than that normally encountered in the unsedated state. Although lightly sedated, the animals were conscious and easily excited by extraneous noise. Measurements were obtained with the animals lying quietly on their right side. All pressure transducers (Statham P23dB) were adjusted to the same height and referenced to the dorsal spine to closely approximate mid heart level. The micromanometer was calibrated at the beginning of each study by matching the systolic pressure to that measured simulta-

![Figure 2. Analog recordings at selected levels of coronary pressure in an individual animal. Each panel represents a single cardiac cycle during a steady-state level of coronary pressure reduction. Mean coronary pressure corresponding to each measurement is illustrated below each panel. Solid vertical lines drawn on the recordings of wall thickness and segment length represent end diastole (ED, onset of positive dP/dt) and end systole (ES, 20 msec before peak negative dP/dt). During gradual pressure reduction produced by inflating the hydraulic occluder, regional circumflex function remained constant over a wide coronary pressure range. When mean coronary pressure fell below 35 mm Hg (diastolic pressure, ~20 mm Hg), further reductions in pressure were associated with large reductions in both segment shortening and wall thickening over a relatively narrow pressure range. After restoration of coronary pressure (right panel), circumflex function remained depressed in a fashion similar to stunned myocardium. Pao, aortic pressure; PLV, left ventricular pressure; PCL, left circumflex pressure; dP/dt, first derivative of left ventricular pressure; LC, left circumflex; LAD, left anterior descending coronary artery.](http://circres.ahajournals.org/doi/10.1161/01.RES.13.6.823)
neously in the ascending aorta and matching left ventricular end-diastolic pressure to equal the peak atrial wave on the simultaneously measured left atrial pressure. Variations in heart rate over the experimental period were minimized by atrial pacing at a rate slightly more than the spontaneous heart rate.

After allowing 30 minutes for the animal to adjust to the laboratory, measurements of hemodynamics and regional function were begun. Progressive reductions in distal circumflex pressure were produced by the hydraulic occluder. Before injecting microspheres, each level of pressure reduction was held constant for at least 5 minutes. Microsphere flow measurements were performed under control circumstances and after coronary pressure reached ~50 mm Hg with maintained regional circumflex function. Additional microspheres were injected during steady-state reductions in coronary pressure, which resulted in measurable reductions in regional circumflex function below resting values.

Regional perfusion was quantified with the reference withdrawal technique. Up to eight flow measurements were performed in individual animals with 15-μm microspheres labeled with the following gamma-emitting nuclides: 153Gd, 51Co, 114In, 113Sn, 95Nb (New England Nuclear, Boston, Massachusetts) and 51Cr, 52Sr, 46Sc (3M Incorporated). Microspheres were injected in 10% dextran and 0.01% Tween 80. The suspensions were placed in an ultrasonicator for at least 15 minutes and vortex agitated before injection. Approximately 2–4 × 10⁶ microspheres were injected into the left atrium over a 10–15-second period and flushed with warm arterial blood. Before microsphere injection, a reference arterial blood sample was started at a constant rate (10 ml/min) from the descending aortic catheter and continued for 2 minutes. Aortic, left ventricular, and coronary artery pressure as well as measurements of regional function were monitored throughout the withdrawal period. Of 71 total microsphere injections, six were discarded because of abruptly altered hemodynamic conditions after microsphere injection. From two to seven injections were acceptable in each animal (n = 7, one dog; n = 6, one dog; n = 5, three dogs; n = 4, six dogs; n = 3, three dogs; n = 2, two dogs). After the experiments were completed, the animals were killed with potassium chloride overdose during deep barbiturate anesthesia. The hearts were removed and placed in formalin for several days to facilitate sectioning.

The left ventricle was sliced into four concentric circumferential rings and the apex discarded. Each ring was cut into eight wedges noting the anatomic location of each wedge. Wedges were then divided into four transmural layers of approximately equal thickness. The papillary muscles were removed and counted separately. The circumflex perfused core included wedges from the base of the heart surrounding the crystals. Flow in samples adjacent to this region were analyzed to ensure that all selected myocardial samples were within the perfused core. Each sample was weighed and activity quantified with a Tracor-Northern sodium iodide detector. Activity of each isotope was determined with a least-squares radionuclide separation technique. Regional myocardial blood flow was calculated as previously described.

Normalization of regional flow. Because of both temporal and spatial heterogeneity of microsphere flow measurements, regional flow responses in the circumflex (LC) region were normalized to flow responses in the left anterior descending (LAD) or control region. This LC/LAD flow ratio reflected the relative reduction in circumflex flow under each experimental condition in a fashion similar to that previously used by other investigators. Under control conditions, the ratio of LC/LAD flow in the endocardium varied among animals (mean, 1.01 ± 0.10; range, 0.86 to 1.21). Because this was believed to reflect sampling variation and spatial heterogeneity, subsequent measurements of the LC/LAD flow ratio were divided by the control ratio. This latter parameter was called the normalized LC/LAD endocardial flow ratio.

Flow measurements associated with a depression in wall thickening and/or segment shortening below 90% of control values were grouped by the level of normalized endocardial flow reduction (71–90%, 71–70%, 31–50%, <30%). To avoid bias, each dog was represented in a given group only once. Multiple flow measurements that fell within the same group for a given dog were averaged along with their corresponding hemodynamic parameters to obtain single values. In animals in which coronary pressure was reduced but regional function unchanged (non-ischemic points), closed-loop autoregulatory gain was calculated as previously described.
Coronary Pressure-Function Relations

Relations between coronary pressure and circumflex function were examined in 16 dogs 15±7 days after instrumentation. Control measurements were performed after a 30-minute equilibration period, after which coronary pressure was gradually reduced in 2–5 mm Hg increments. At least 2 minutes were allowed for coronary pressure and regional function to equilibrate before data sampling. When function began to fall, coronary pressure was reduced over smaller increments (1–2 mm Hg) until percent wall thickening approached zero, after which pressure was restored. With this approach, 10–54 steady-state points were available for analysis in individual animals.

Normalization of circumflex function. To compare relative reductions in circumflex function among different animals, circumflex wall thickening (%WT) and segment shortening (%SS) were normalized. Preliminary studies indicated that regional dysfunction was never observed at a coronary pressure more than 50 mm Hg under these hemodynamic conditions. Therefore, all measurements of %WT and %SS at mean coronary pressures more than 50 mm Hg were averaged to obtain the control value of circumflex function for each individual study. Each individual measurement of %WT and %SS in a given experiment was then divided by this mean value and expressed as a percent. Because of the small variability in control function with repeated measurements (coefficient of variation, 3–4%), significant reductions in function were defined as those having both a mean coronary pressure below 50 mm Hg as well as a value of normalized function less than 90% of control. Pressure-function data fulfilling these criteria were fit to linear and quadratic relations. Pressures corresponding to 100%, 50%, and 0% of control function were calculated with the coefficients obtained from the least-squares fit and tabulated. To avoid errors related to extrapolation, animals were excluded from regression analysis if the degree of coronary pressure reduction did not result in function falling below 50% of control values. In addition, studies in which the coefficient of variation for systemic hemodynamics and/or control function exceeded 10% were excluded because hemodynamic instability could alter myocardial metabolic demand during the study period.

Data Analysis

Experimental data were recorded on an eight-channel Gould 2800 W recorder at a paper speed of.
FiguRe 4. Plot of relation between normalized endocardial flow and coronary pressure. Endocardial flow remained constant until mean coronary pressure (●) fell below 40 mm Hg. Corresponding values of mean diastolic coronary pressure (○) and end-diastolic coronary pressure (△) were 30 and 25 mm Hg, respectively. Pressure range over which endocardial flow approached zero varied from ~20 mm Hg for mean coronary pressure to ~10 mm Hg for end-diastolic coronary pressure. Endocardial autoregulatory relation was shifted to the left when flow was related to diastolic coronary pressure indexes as opposed to mean coronary pressure. Values are mean±SEM.

100 mm/sec. All data were digitized at a sampling rate of 200 Hz with a Data Translation DT 2801-A analog-to-digital convertor (Marlborough, Massachusetts) interfaced to an IBM PC AT computer. Most experiments were digitized and analyzed online; however, in some, analog signals were recorded on a Hewlett-Packard FM tape recorder (Palo Alto, California) and digitized off-line. All data represent averages of a 15-second sampling interval comprising at least 20 cardiac cycles.

Signals from the ultrasonic crystals were processed with a Triton Technology (San Diego, California) 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 Δ SL = EDSL - ESSL. Percent wall thickening and percent segment shortening were determined as follows: %WT = Δ WT/EDWT and %SS = Δ SL/EDSL.

Constancy of systemic hemodynamics throughout each study was determined by measuring heart rate, mean aortic pressure, systolic and end-diastolic left ventricular pressure, and the first derivative of left ventricular pressure (peak + dP/dt and peak - 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 when 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.

Statistical Analysis

All values represent the mean±SD unless otherwise indicated. Data for microsphere flow measurements were analyzed with one-way analysis of variance. Significant differences between each level of stenosis and the corresponding control values were determined with a two-tailed paired t test. A value of p<0.05 was considered significant.

Regression analyses of flow-function and pressure-function relations were performed with a least-squares linear fit. In some instances, second-order polynomials and exponential least-squares fits similar to previous studies8,9 were also determined. Statistical significance between different regression lines as well as between linear and quadratic fits was determined with an analysis of covariance.23

Results

Analog recordings from an individual experiment are illustrated in Figure 2. Regional circumflex wall thickening and segment shortening remained con-

FIGURE 5. Plots of the relation between endocardial function and transmural flow at selected levels of coronary stenosis corresponding to data obtained in microsphere flow experiments. Control points have been eliminated for clarity. --- , Lines of identity (i.e., a one-to-one relation between reductions in flow and function). Reductions in both segment shortening and wall thickening were closely related to reductions in endocardial flow (●). In contrast, changes in endocardial function were dissociated with epicardial flow (○). Values are mean±SEM.
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TABLE 2. Microsphere Flow Experiments: Regional LC Function

<table>
<thead>
<tr>
<th>Group (% Control endo flow)</th>
<th>Normalized LC:LAD endo flow</th>
<th>%LC WT (%)</th>
<th>%LC SS (%)</th>
<th>LC ED WT (mm)</th>
<th>LC ED SL (mm)</th>
<th>LC Δ WT (mm)</th>
<th>LC Δ SL (mm)</th>
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<tr>
<td>Nonischemic (n = 10)</td>
<td>C</td>
<td>1</td>
<td>28.9 ± 11.4</td>
<td>18.4 ± 8.1</td>
<td>9.89 ± 1.0</td>
<td>14.59 ± 2.54</td>
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<td>S</td>
<td>1.03 ± 0.15</td>
<td>28.4 ± 11.6</td>
<td>17.9 ± 5.4</td>
<td>10.02 ± 1.1</td>
<td>14.50 ± 2.56</td>
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<td></td>
<td>p</td>
<td>NS</td>
<td>NS</td>
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<td>&lt;0.003</td>
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<tr>
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<td>n</td>
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<td>8</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>6</td>
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<tr>
<td></td>
<td>71-90% (n = 9)</td>
<td>C</td>
<td>1</td>
<td>24.9 ± 8.0</td>
<td>16.7 ± 4.4</td>
<td>10.79 ± 1.83</td>
<td>12.56 ± 2.73</td>
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<td></td>
<td>S</td>
<td>0.82 ± 0.07</td>
<td>22.7 ± 8.2</td>
<td>12.5 ± 4.7</td>
<td>10.92 ± 1.85</td>
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<td>p</td>
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<td>&lt;0.005</td>
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<td>51-70% (n = 7)</td>
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<td>31-50% (n = 5)</td>
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<td>NS</td>
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Values are mean ± SD.

Normalized LC:LAD endo flow, normalized endocardial flow for total perfused region (see text for details); %LC WT, circumflex wall thickening (%); % LC SS, circumflex segment shortening (%); ED WT, end-diastolic wall thickness; ED SL, end-diastolic segment length; Δ WT, end-systolic minus end-diastolic wall thickness; Δ SL, end-systolic minus end-systolic segment length; n, number of measurements in each group; C, control; S, stenosis; p, statistical significance for two-tailed paired t test; NS, not significant. Measurements have been grouped into five levels of pressure and flow reduction as described in the text.

stant over a wide range as coronary artery pressure was reduced. In this animal, there were no changes in function until coronary pressure fell below 35 mm Hg (end-diastolic coronary pressure, 20 mm Hg). Below this critical pressure, reductions in coronary pressure were associated with pronounced reductions in circumflex function over a relatively narrow pressure range. Despite the reductions in circumflex function, there were no major changes in systemic hemodynamics. As noted in the extreme righthand panel of this figure, circumflex function remained depressed below control after occlusion release. In 10 animals, function was compared before and after determination of the autoregulatory relation. On restoration of coronary pressure after an average of 41 ± 18 (SD) minutes of ischemia, circumflex wall thickening fell from 26.8 ± 7.0% to 21.7 ± 6.0% (p < 0.002) and segment shortening fell from 18.3 ± 4.9% to 12.4 ± 5.1% (p < 0.001). There were no significant changes in anterior descending function. Thus, despite restoration of coronary pressure and presumably flow after the determination of the autoregulatory relation, wall thickening was depressed to 81 ± 13% of control and segment shortening to 66 ± 19% of control and recovered over the subsequent 24-hour period.

**Transmural Coronary Autoregulation**

Under control conditions for all animals (n = 16), heart rate averaged 106 ± 14 beats/min. Aortic pressure was 109 ± 9 mm Hg systolic and 74 ± 7 mm Hg diastolic. Left ventricular end-diastolic pressure averaged 5.7 ± 2.9 mm Hg. Left ventricular dP/dt max was 3,061 ± 606 mm Hg/sec and dP/dt min was −2,556 ± 351 mm Hg/sec. There were no significant differences in systemic hemodynamics comparing control with corresponding stenosis measurements except for heart rate, which increased from 100 to 107 beats/min when circumflex flow fell to less than 30% of control (p < 0.05). Circumflex zone wall thickening averaged 26.7 ± 10.5%, and segment shortening averaged 17.8 ± 4.8%. In the anterior descending or control zone, wall thickening averaged 28.4 ± 9.8%, and segment shortening averaged 24.8 ± 4.8%. Arterial blood gases at the time of study were pH, 7.41 ± 0.04; Po2, 75 ± 6 mm Hg; and PaCO2, 33 ± 4 mm Hg. Hematocrit averaged 35 ± 5%.

Regional autoregulatory relations at six selected levels of endocardial flow reduction are illustrated...
NORMALIZED WALL THICKENING (% Control)

NORMALIZED SEGMENT SHORTENING (% Control)

NORMALIZED ENDO FLOW (% Control)

in Figure 3. Corresponding hemodynamic and regional flow measurements are summarized in Table 1. Under control conditions, circumflex endocardial flow for all animals averaged 1.06 ± 0.22 ml/min/g and epicardial flow averaged 0.82 ± 0.24 ml/min/g (p<0.001). There were no significant differences in flow between the circumflex or the anterior descending region under resting conditions. When regional function was maintained as coronary pressure was reduced from 84 ± 10 to 49 ± 8 mm Hg, the reduction in absolute flow was 6% for the endocardium and 8% for the epicardium (p = NS). With the changes in absolute flow and mean coronary pressure for these nonischemic points, closed-loop autoregulatory gain was 0.86 for the endocardium and 0.80 for the epicardium. Endocardial flow began to fall significantly when coronary pressure reached 37 mm Hg (p<0.001 vs. control). This was associated with a corresponding fall in the endocardial-to-epicardial flow ratio from 1.34±0.15 to 1.14±0.19 (p<0.005 vs. control). In contrast to the endocardium, autoregulation of epicardial flow was maintained until mean coronary pressure fell to 25 mm Hg (p<0.02 vs. corresponding control measurements). There were no significant changes in anterior descending endocardial or epicardial flow during circumflex ischemia.

Normalized circumflex endocardial flow for each level of stenosis is plotted versus mean, mean diastolic, and end-diastolic coronary pressure in Figure 4. The endocardial autoregulatory relation was qualitatively similar for each index of distal coronary pressure. The autoregulatory relations with end-diastolic and mean diastolic coronary pressure were, however, shifted to the left of the autoregulatory relation for mean coronary pressure. Furthermore, the range of coronary pressure over which endocardial flow fell with diastolic pressure indexes was narrower.

Flow-Function Relation During Autoregulation

Figure 5 contrasts endocardial and epicardial variations in flow relative to endocardial function. Table 2 summarizes measurements of regional function. Reductions in both segment shortening and wall thickening were closely related to reductions in endocardial flow. In contrast, epicardial flow remained unchanged until the most severe level of stenosis, despite large reductions in endocardial function. These data indicate a close coupling of endocardial flow with function measured by wall thickening or segment shortening. Furthermore, despite the fact that wall thickening is a transmural measurement, its dissociation with epicardial flow was similar to that of segment shortening.

Regeneration relations for both wall thickening and segment shortening reductions are illustrated in Figure 6. Reductions in function (percent of control) were correlated with flow (percent of control) in the endocardial sample containing the individual crystals. Flow-function relations with the circumflex core region flows were not statistically different. The relation between wall thickening reductions (y) and endocardial flow (x) as a percent of control was described by a linear equation:

\[ y = 0.96x + 3.9, \quad n = 60, \quad r = 0.90. \]

A quadratic equation significantly improved the fit of the wall thickening data:

\[ y = -0.0103x^2 + 2.34x - 33.5, \quad r = 0.93, \quad p<0.001 \text{ versus linear fit by analysis of covariance}. \]

An exponential equation failed to fit the data and

\[ y = 0.96x + 3.9, \quad r = 0.90. \]

Relation was improved by a second-order polynomial

\[ y = -0.0103x^2 + 2.34x - 33.5, \quad r = 0.93, \quad p<0.001 \text{ versus linear fit by analysis of covariance}. \]
also failed to define the control point (100% function, 100% flow). Despite the improved quadratic fit over the entire range of endocardial flow reduction, the linear fit was within 10% of the quadratic fit at levels of flow above 30%. Thus, from a practical standpoint, reductions in endocardial flow in this range were related to reductions in wall thickening on a nearly one-to-one basis.

The relation between reductions in segment shortening \((y)\) and endocardial flow \((x)\) was also linear (Figure 6): \(y = 1.41x - 42.7, n = 43, r = 0.92\). The fit was not improved significantly by a quadratic equation, and an exponential equation did not fit the data. As with wall thickening, flow-function relations based on core region flows were not statistically different. However, in comparison to wall thickening, there were greater reductions in segment shortening at any given level of flow reduction \((p < 0.001\) for the slope of the linear fits).

Figure 7 depicts normalized wall thickening and segment shortening reductions at comparable levels of ischemia in dogs in which both pairs of crystals were operational and appropriately aligned. The relation between segment shortening \((y)\) and wall thickening \((x)\) reductions as a percent of control was described by the following equation: \(y = 1.36x - 40.1, n = 380, r = 0.95\). Akinetic of segment length \((y = 0%)\) occurred at a time when wall thickening persisted \((x = 29.5%\) of control). Thus, these data corroborate the finding that reductions in segment shortening exceed wall thickening reductions during steady-state circumflex ischemia.

**Coronary Pressure-Function Relations**

Coronary pressure-function relations were similar to endocardial autoregulatory relations based on relative reductions in coronary flow. Figure 8 illustrates typical pressure-function relations obtained in an individual animal for both wall thickening and segment shortening. In each animal, regional function remained constant over a wide range of coronary artery pressure. Below a critical pressure, reflecting the lower limit of endocardial autoregulation, there was a linear fall in function with pressure. The reproducibility of the pressure-function relation over time is shown in Figure 9. Here, pressure-function relations were constructed on six different days over a period of 4 weeks in the same animal. Heart rate \((118 \pm 5\) beats/min) and systolic pressure \((113 \pm 5\) mm Hg) remained within fairly narrow limits over this time. The lowest pressure at which regional function was maintained averaged 44.9 \(\pm\) 3.3 mm Hg for wall thickening and 45.5 \(\pm\) 3.2 mm Hg for segment shortening. The slope of the pressure-function relation below this lower pressure limit averaged 4.81 \(\pm\) 1.14%/mm Hg \((r = 0.98 \pm 0.02)\) for wall thickening and 8.83 \(\pm\) 2.20%/mm Hg \((r = 0.98 \pm 0.01)\) for segment shortening. Thus, there was close correlation of pressure and function throughout the duration of the study with a lower autoregulatory limit that was reproducible within narrow bounds.

Pressure-function regression relations for all animals are summarized in Table 3, and corresponding pressure-function points are plotted in...
NORMALIZED WALL THICKENING (% Control)

DAY FOLLOWING INSTRUMENTATION

MEAN CORONARY PRESSURE (mm Hg)

Figure 10. The stability of control hemodynamics was ascertained with the coefficient of variation (Table 4). This ranged from 1% to 6% for the different variables examined indicating that over the time period of the pressure-function determination, global determinants of myocardial demand were essentially constant. Among all animals, the correlation coefficient for the regression of mean coronary pressure and function averaged 0.94 ± 0.05 for wall thickening reductions and 0.96 ± 0.03 for segment shortening reductions. A quadratic relation did not improve the fits and frequently could not be extrapolated back to 100% function. Wall thickening began to fall (100% function) below a mean coronary pressure of 38.9 ± 5.6 mm Hg, reaching a point of akinesis (0% function) at a pressure of 21.1 ± 3.5 mm Hg. Segment shortening began to fall at a mean coronary pressure of 41.7 ± 7.4 mm Hg (p < 0.056 vs. wall thickening) and reached a point of akinesis at a mean coronary pressure of 26.2 ± 3.8 mm Hg (p < 0.006 vs. wall thickening). Using diastolic indexes of coronary pressure, the pressure-function relations were shifted to the left. Wall thickening began to fall at a mean diastolic pressure of 29.8 ± 5.6 mm Hg and at an end-diastolic pressure of 22.0 ± 2.9 mm Hg. Segment shortening began to fall when mean diastolic pressure reached 31.9 ± 8.1 mm Hg (p < 0.062 vs. wall thickening) and end-diastolic pressure reached 24.5 ± 3.7 mm Hg (p < 0.062 vs. wall thickening). The slope of the pressure-function relation increased when mean diastolic pressure and end-diastolic pressure were used. This reflected the fact that the pressure range over which function fell from 100% to 0% of control became narrower (~10 mm Hg for end-diastolic coronary pressure).

Discussion

This study indicates that the coronary pressure-function relation can be used to define the lower limit of endocardial autoregulation. In contrast to anesthetized animals, in which endocardial autoregulatory reserve is exhausted at coronary pressures of 70 mm Hg, endocardial flow and function remain constant in conscious animals until coronary pressure falls to 40 mm Hg. As outlined below, this substantial shift in the lower autoregulatory limit is difficult to explain on the basis of differences in hemodynamic factors influencing myocardial metabolic demand or vasodilator reserve. This raises the possibility that other factors may be responsible for modulating coronary autoregulation in the open-chest anesthetized animal.
TABLE 3. Pressure-Function Experiments: Coronary Pressure-Function Relations

<table>
<thead>
<tr>
<th>Abscissa parameter</th>
<th>Normalized LC WT (n = 14)</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC pressure (mm Hg)</td>
<td>Mean</td>
<td>38.9±5.6</td>
<td>21.1±3.5</td>
<td>6.36±2.35</td>
</tr>
<tr>
<td></td>
<td>Mean diastolic</td>
<td>29.8±5.6</td>
<td>14.1±3.7</td>
<td>7.29±2.74</td>
</tr>
<tr>
<td></td>
<td>End-diastolic</td>
<td>22.0±2.9</td>
<td>12.2±2.5</td>
<td>11.39±3.69</td>
</tr>
<tr>
<td></td>
<td>Normalized LC SS (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC pressure (mm Hg)</td>
<td>Mean</td>
<td>41.7±7.4</td>
<td>26.2±3.8*</td>
<td>7.69±3.16</td>
</tr>
<tr>
<td></td>
<td>Mean diastolic</td>
<td>34.0±4.7*</td>
<td>18.7±3.1*</td>
<td>9.23±3.81</td>
</tr>
<tr>
<td></td>
<td>End-diastolic</td>
<td>24.5±3.7</td>
<td>15.5±2.01</td>
<td>12.7±5.27</td>
</tr>
</tbody>
</table>

Values represent mean±SD. 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). The slope (percent/mm Hg) and intercept (%) represent the mean linear coefficients from the pressure-function relation for each abscissa parameter and r is the linear correlation coefficient. A total of 22 pressure-function relations were suitable for analysis. In animals in which multiple pressure-function relations were obtained, the points corresponding to 100%, 50%, and 0% function were determined for each relation and then averaged. In addition, the slope and the intercept for each relation were averaged to obtain one value.

*<p<0.01 vs. corresponding wall thickening values; t<p<0.05 vs. corresponding wall thickening values.

Coronary Pressure-Function Relation

In view of the close relation between endocardial flow and function during myocardial ischemia, it is not surprising that the relation between endocardial function and coronary pressure is similar to the endocardial autoregulatory relation between flow and pressure. This correspondence permits the steady-state coronary pressure-function relation to be used to characterize endocardial autoregulation at any point in time, as well as before and after specific interventions. Furthermore, under experimental circumstances in which oxygen extraction increases as coronary pressure is reduced, the pressure-function relation may allow more precise interpretation of flow changes in terms of the adequacy of endocardial oxygen delivery.

Both endocardial segment shortening and transmural wall thickening remained constant over a wide range of coronary pressure within individual animals (coefficient of variation, 3-4%). Below the lower autoregulatory limit, function fell in a linear fashion with further reductions in coronary pressure (although a second-order term occasionally improved the data fit, the second-order fit deviated in an unphysiological fashion outside of the data range). Reductions in function correlated best with...
TABLE 4. Pressure-Function Experiments: Systemic Hemodynamics, Regional Function, and Coefficients of Variation (n=16)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Coefficient of variation (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>108 ± 18</td>
<td>2.7 ± 2.3%</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>113 ± 11</td>
<td>2.8 ± 1.1%</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74 ± 8</td>
<td>4.8 ± 2.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>91 ± 8</td>
<td>3.6 ± 1.1%</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.7 ± 4.0</td>
<td>*</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>3,095 ± 527</td>
<td>5.9 ± 2.6%</td>
</tr>
<tr>
<td>Min</td>
<td>−2,535 ± 321</td>
<td>−6.3 ± 1.9%</td>
</tr>
<tr>
<td>Regional Function (P&lt;0.5 mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC WT % WT (n=14)</td>
<td>26.0 ± 8.2</td>
<td>3.8 ± 2.6%</td>
</tr>
<tr>
<td>ED (mm)</td>
<td>9.29 ± 1.34</td>
<td>0.9 ± 0.5%</td>
</tr>
<tr>
<td>ES (mm)</td>
<td>11.66 ± 1.78</td>
<td>0.8 ± 0.5%</td>
</tr>
<tr>
<td>LC SL % SS (n=11)</td>
<td>17.2 ± 4.4</td>
<td>2.9 ± 3.1%</td>
</tr>
<tr>
<td>ED (mm)</td>
<td>14.45 ± 2.85</td>
<td>0.4 ± 0.4%</td>
</tr>
<tr>
<td>ES (mm)</td>
<td>11.88 ± 2.02</td>
<td>0.8 ± 0.8%</td>
</tr>
<tr>
<td>LAD WT % WT (n=14)</td>
<td>25.5 ± 9.8</td>
<td>3.3 ± 2.1%</td>
</tr>
<tr>
<td>ED (mm)</td>
<td>8.78 ± 2.09</td>
<td>0.7 ± 0.6%</td>
</tr>
<tr>
<td>ES (mm)</td>
<td>11.03 ± 2.60</td>
<td>0.8 ± 0.5%</td>
</tr>
<tr>
<td>LAD SL % SS (n=10)</td>
<td>24.8 ± 4.8</td>
<td>2.8 ± 2.1%</td>
</tr>
<tr>
<td>ED (mm)</td>
<td>16.12 ± 4.22</td>
<td>1.0 ± 0.7%</td>
</tr>
<tr>
<td>ES (mm)</td>
<td>12.13 ± 3.24</td>
<td>0.9 ± 0.6%</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LV dP/dt, first derivative of LV pressure; LC, left circumflex; LAD, left anterior descending; WT, wall thickness; SL, segment length; %WT, wall thickening (see text for calculation); %SS, segment shortening (see text for calculation); ED, end diastole; ES, end systole.

*For LVEDP, the standard deviation of LVEDP within an experiment averaged 1.8 ± 1.3 mm Hg.

mean coronary pressure (r = 0.94 for wall thickness, r = 0.96 for segment length). They also correlated closely with mean diastolic and end-diastolic coronary pressure (r = 0.90–0.95, Table 3). Although reductions in segment shortening appeared to begin at slightly higher coronary pressures than reductions in wall thickening (42 vs. 39 mm Hg), the level of significance of the difference was borderline (p<0.056).

The temporal reproducibility of coronary autoregulation is currently unknown but has potential importance in interpreting studies examining changes in coronary flow over time. In addition to variations in heart rate, factors that alter systemic pressure, oxygen carrying capacity, or neural tone are likely to alter the overall autoregulatory relation. In the present study, in which heart rate and systolic pressure remained within narrow bounds, there was minimal day-to-day variation in the coronary pressure-function relation up to 5 weeks after surgical instrumentation. These results suggest fairly constant characteristics of endocardial autoregulation over this time period.

Reproducibility of the pressure-function relation in short-term studies is more problematic than on a day-to-day basis. Pressure-function relations in the present study were constructed with progressive reductions in coronary pressure. Although the experimental procedure resulted in regional dysfunction and ischemia for only short periods, regional function remained depressed below control by 20–30% on restoration of normal coronary pressure. Regional function returned to control levels within 24 hours, and gross evidence of myocardial infarction was not observed. The depression in function appeared similar to the reversible postischemic dysfunction reported after brief periods of total coronary occlusion or prolonged partial occlusion. This finding highlights an important methodologic consideration in studying autoregulation and/or the pressure-function relation on a repeated basis at a single setting, that is, effects of interventions can only be evaluated after allowing a sufficient time period for endocardial function to recover after preintervention data have been collected. This issue may be germane to the interpretation of previous studies examining the role of interventions during autoregulation in anesthetized animals. Characteristics of autoregulation in the postischemic or "stunned" state may differ and contribute to the general lack of reproducibility of autoregulation observed in individual anesthetized animals.

Two additional factors need to be addressed when using the coronary pressure-function relation
Transmural Variations in Autoregulation

The results of this study are consonant with previous studies in anesthetized animals demonstrating transmural variations in autoregulation and vulnerability of the endocardium to ischemia. They differ, however, in terms of the degree to which flow, oxygen delivery, and function remain constant above the lower endocardial autoregulatory pressure limit and the level of coronary artery pressure at which autoregulation is exhausted (as manifest by a decline in flow and function).

Investigators from several laboratories have attempted to quantify the degree to which flow remains constant during autoregulation by calculating the closed-loop autoregulatory gain. In the present study, the small variations in absolute flow (6–8%, p = NS) observed when coronary pressure was reduced from 84 to 49 mm Hg resulted in values of closed-loop gain ($G_c$) of 0.86 for the endocardium and 0.80 for the epicardium. Direct comparison with results from anesthetized studies is difficult because transmural variations in $G_c$ have not been reported. Available measurements based on epicardial artery flow changes vary markedly, depending on the coronary pressure range examined. Dole and Nunno have also demonstrated that increases in heart rate from 40 to 120 beats/min increase $G_c$ significantly. In general, however, most anesthetized studies report considerably lower values of $G_c$ than the present study over a similar pressure range (i.e., $G_c<0.5$).

The comparison of the present values of $G_c$ with previous results is further complicated by the finding that myocardial oxygen consumption decreases as coronary pressure is reduced over the autoregulatory plateau in some anesthetized studies. This variation was originally described by Gregg and suggests that under some circumstances, coronary pressure and/or flow appear to determine myocardial oxygen consumption. While oxygen consumption was not measured in the present study, the fact that both endocardial function and oxygen delivery remained unchanged over a wide range of distal coronary pressure argues against such an effect. Thus, the generally higher values of $G_c$ in comparison to those in anesthetized animals may reflect both a lower resting coronary venous $P_O_2$ (and less reliance on enhanced oxygen extraction) as well as the absence of the Gregg effect as coronary pressure is reduced.

The lower autoregulatory pressure limit has traditionally been believed to reflect the critical pressure at which endocardial vasodilator reserve is exhausted. Reductions in the time available for endocardial perfusion with increased rate and increases in myocardial metabolic demand both cause this limit to rise. Recent studies have also demonstrated reductions in flow during autoregulation in the presence of pharmacologically recruitable vasodilator reserve in anesthetized animals. Although the presence of pharmacological vasodilator reserve was not examined in the present study, it is difficult to attribute the lower endocardial autoregulatory pressure limit in the present study (40 vs. 70 mm Hg) to mean pressure and 25 vs.
50 mm Hg (diastolic pressure) to differences in resting flow and/or endocardial vasodilator reserve between anesthetized and unanesthetized animals for several reasons. First, despite somewhat higher heart rates, values of resting endocardial flow in previous anesthetized studies are similar to those in the present study (~1 ml/min/g). This may reflect a reduction in contractility in the anesthetized state that counteracts the effects of increased rate on myocardial demand. Second, differences in heart rate between the present study and previous studies are modest (~100 vs. ~150 beats/min). Autoregulatory reductions in flow at pressures as high as 70 mm Hg are difficult to reconcile with measurements of endocardial vasodilator reserve at a rate of 150 beats/min demonstrating flows of 4.1 ml/min/g at a pressure of ~90 mm Hg. In addition, a preliminary report from our laboratory in awake animals has demonstrated a lower autoregulatory limit of less than 70 mm Hg in the face of even higher heart rate (200 beats/min) and higher resting flow (1.5 ml/min/g). Finally, in contrast to endocardial flow, epicardial flow appears to be independent of heart rate during maximum vasodilation. Nevertheless, the lower limit of epicardial autoregulation is also higher in the anesthetized animal (~40 mm Hg) as opposed to the present study (25 mm Hg).

Studies of autoregulation in other vascular beds have demonstrated attenuated autoregulation in response to anesthetic agents. It is therefore possible that effects of anesthesia and/or acute surgical instrumentation alter coronary autoregulatory responses as they do the relation between endocardial flow and function. In this regard, the present data are of particular interest in comparison to the study of Gallagher et al. where coronary pressure and wall thickening were examined during myocardial ischemia in anesthetized open-chest dogs (Figure 11). The experimental preparation was similar to the present study. Systolic pressure levels were similar, but heart rate was slightly higher (130 vs. 100 beats/min). Despite lower control endocardial flows in the anesthetized animals (0.62 vs. 1.05 ml/min/g in the present study), reductions in flow began at significantly higher coronary pressures. An ~20% reduction in endocardial flow occurred at a mean coronary pressure of 55 versus 37 mm Hg in the present study. Reductions in endocardial flow in each study were associated with concomitant reductions in wall thickening, even though control values of wall thickening were lower in the anesthetized
animals (19.3% vs. 28.9%). The shift to the left in both the endocardial autoregulatory and the pressure-function relations in the present study supports the hypothesis that factors other than systemic hemodynamics produce differences in coronary autoregulation during anesthesia. These differences warrant further investigation and may bear importantly on the extrapolation of data obtained in anesthetized animals to humans.

**Endocardial Flow-Function Relation**

It has been appreciated since the classic study of Tennant and Wiggers in 1935 that myocardial performance is closely coupled to coronary flow. Although function falls when flow is reduced to a critical level, reported myocardial flow-function relations exhibit considerable variability. While some of this variation no doubt relates to anesthesia, differences also exist between endocardial flow-function relations obtained in conscious animals when function is assessed by transmural wall thickening as opposed to segment shortening. Although beat-to-beat variations in wall thickening and segment shortening during temporary total coronary occlusion have been reported to follow a one-to-one relation, correlative studies during steady-state ischemia have not previously been reported. Based on the present results, there appear to be quantitative differences between the magnitude of wall thickening and segment shortening reduction at comparable levels of ischemia. Flow-function relations from the present study are compared with two previous studies in conscious dogs in Figure 12.

Wall thickening and endocardial flow were closely coupled in a fashion similar to that reported by Gallagher et al. In each study, the flow-function relation was mildly curvilinear and better described by a second-order polynomial than a linear fit. Although the linear relations differ modestly in slope (Figure 12A), the curvilinear relations from the two studies (Panel B) are quite similar. The linear difference may reflect the fact that relatively few measurements were performed in the present study during severe ischemia. When endocardial flow was more than 30% of control, deviations of quadratic from linear fits were small (<10%). Thus, during mild to moderate ischemia, relative reductions in normalized wall thickening provide a useful index of the relative reduction in endocardial flow on a nearly one-to-one basis.

Although segment shortening reductions were also closely coupled to endocardial flow, the quantitative relation between the two parameters in the present study differed from that previously reported in conscious animals by Vatner (Figure 12C). In the present study, the relative magnitude of segment shortening reduction exceeded that of endocardial flow reduction and was linear (Figures 5 and 6). The previous study found the flow-function relation to be exponential, with a 50% reduction in flow resulting in only a ~20% reduction in segment shortening. This would seem to indicate a relative insensitivity of segment shortening reductions during mild to moderate ischemia in contrast to the present findings. While it is difficult to reconcile the difference in terms of methodology, regional variations in the endocardial flow-function relation may be responsible. Segment shortening in the present study was measured in the posterobasal free wall (distal circumflex artery) as opposed to the anteropapical free wall (anterior descending artery) in the earlier study. Observations in anesthetized animals indicate that relations between epicardial segment shortening and flow during myocardial ischemia differ between the two regions. Additional difference between the studies may relate to the fact that resting coronary flow levels were somewhat higher in the earlier study, despite similar global determinants of myocardial oxygen demand. Thus, differences in autoregulatory gain between the two studies could conceivably have altered the flow-function relation, particularly if oxygen delivery at reduced flow were maintained by increasing extraction in the earlier study.

Previous studies examining relations between regional function and endocardial flow have not compared simultaneous measurements of wall thickening and endocardial segment shortening during steady-state myocardial ischemia. The present study indicates that the magnitude of reduction in segment shortening is more than that of wall thickening during steady-state circumflex ischemia. Akinetic (i.e., absence of systolic shortening) occurred at a time when wall thickening, while significantly reduced, was still present (Figure 7). In terms of detecting the onset of endocardial ischemia, segment shortening began to fall at a slightly higher mean coronary pressure (42 vs. 39 mm Hg), but the difference was of borderline significance (p < 0.056). Thus, while the magnitude of segment shortening impairment is more than wall thickening at comparable levels of ischemia, there appears to be little difference between the measurements in terms of detecting the lower autoregulatory pressure limit using the coronary pressure-function relation.

**Summary**

The close relation of both endocardial flow and function with coronary pressure demonstrated in this study provides a basis for the use of the coronary pressure-function relation to characterize endocardial autoregulation on a repeated basis in the unanesthetized animal. The characteristics of transmural coronary autoregulation in the unanesthetized animal appear to differ from the anesthetized animal in several respects, with the mean coronary pressure at which endocardial flow begins to fall being considerably lower (40 vs. 70 mm Hg). Although some of the disparity between conscious and anesthetized animals may reflect variations in myocardial metabolic demand and/or vasodilator reserve, factors modulating the coronary autoregulatory mechanism during...
anesthesia seem likely to be operative. Future studies with pressure-function as well as pressure-flow relations should clarify the functional significance of factors that can modulate endocardial autoregulation under different experimental circumstances.

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J M Canty, Jr

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