A Canine Model of Acute Coronary Artery Stenosis: Effects of Deliberate Hypotension

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Coronary artery disease is considered a contraindication to inducing hypotension during surgery because the combined effects of stenosis and hypotension in reducing distal coronary artery perfusion pressure might produce myocardial ischemia. To study the effect of deliberate hypotension (mean systemic pressure, 50 mmHg) on regional myocardial perfusion, oxygenation, and lactate extraction, we constricted the left-anterior descending coronary artery (LADCA) in dogs. Two degrees of stenosis were studied: “critical” stenosis, which reduced resting coronary blood flow by 40%, LADCA pressure was measured distal to the stenosis, and LADCA pressure was obtained by subtracting the left ventricular end-diastolic pressure from the coronary artery diastolic pressure measured past the stenosis. Hypotension was induced by administering sodium nitroprusside, halothane at 1% concentration, or trimethaphan. Lactate extraction and oxygen consumption were measured across the myocardium distal to the stenosis (from the coronary artery to the great cardiac vein) and across the whole heart (from the coronary artery to the coronary sinus). Regional myocardial blood flow was measured using radioactive microspheres. A transmural electrocardiogram was obtained from electrodes implanted in the subendocardium and the subepicardium in the distribution of the LADCA distal to the stenosis. Although the combination of critical stenosis and hypotension reduced regional myocardial blood flow and lowered LADCA perfusion pressure to 27 ± 3 (SE) mmHg, myocardial ischemia did not occur, as evidenced by unchanged lactate extraction and no redistribution of transmural blood flow or change in ST segment. On the other hand, the combination of severe stenosis and hypotension reduced LADCA perfusion pressure to 17 ± 2 (SE) mmHg and produced evidence of ischemia by regional lactate production, reduction of the subendocardial/subepicardial flow ratio, and depression of the ST segment.

For certain surgical procedures, deliberately inducing hypotension during anesthesia facilitates surgery and reduces blood loss.1-3 However, ischemic heart disease is considered a contraindication to such a technique because the combination of hypotension and a narrowed coronary artery would reduce coronary artery blood flow and myocardial oxygen supply.4 This reasoning constitutes the only basis for such a contraindication because no definitive evidence exists. To investigate the effects of deliberate hypotension in the presence of coronary artery stenosis, we developed an acute animal model that permits us to make invasive measurements in the myocardium and in its circulation in animals with induced coronary artery stenosis.

An ideal model would provide 1) a method for determining the degree of stenosis induced; 2) a method for measuring regional oxygen supply and demand; and 3) a sensitive method for detecting myocardial ischemia.

This report details the development of an animal model of induced coronary artery stenosis. Using this model, we examined the effects of drug-induced hypotension. To test this model, we induced hypotension using three contrasting drug techniques, known to produce widely different hemodynamic effects. We present this study in two parts. In the first part, we employed a “critical” stenosis as defined in the literature.5,6 The degree of stenosis, combined with deliberate hypotension, failed to produce evidence of regional myocardial ischemia. In the second part we employed a more severe stenosis that reduced resting cerebral blood flow by 40%. Regional ischemia occurred when this severe stenosis was combined with deliberate hypotension induced by any of the hypotensive agents employed.

Materials and Methods

Anesthesia

In 18 mongrel dogs, (mean weight 27.2 ± 1.9 SE kg), we induced anesthesia with sodium thiopental (25 mg kg⁻¹), relaxed muscles with pancuronium bromide,
We present a method for developing coronary artery stenosis and hypotension. Using an adjustable plastic stenosis device, were placed adjacent to each other on a portion of the LADCA 2-6 cm from its origin. The portion of the LADCA selected was free of branches. We inserted silastic pressure catheters (0.28 mm ID × 0.6 mm OD) into both the GCV and the LADCA distal to the stenosis using a modified Hartmann technique. The undamped frequency response of this catheter system was uniform to 20–25 Hz, and the damping ratio was 0.50–0.50. Silver wires, placed in the subendocardium and subepicardium using the method described by Guyton, were used to record transmural electrocardiographic data. The transmural location of these wires, which were placed in the area of myocardium supplied by the LADCA, was verified by direct observation after the experiment. The wires were connected to a standard electrocardiographic lead system and were read on lead I; the left-arm lead was connected to the subendocardial wire, and the right arm lead was connected to the subepicardial wire. A calibrated micromanometer transducer-tipped catheter (Millar Instrument) was inserted into the left ventricle, and a stiff number 8 polypropylene catheter was placed in the central aorta via the femoral arteries. Figure 1 depicts the surgical preparation.

**Measurements**

Continuous measurements were made of blood pressures in the central aorta, left ventricle (LV), coronary sinus, left atrium, central aorta, and of LADCA phasic and mean blood flow. Maximum positive LV dP/dt was measured by differentiating the left ventricular pressure signal with an active differentiator. The positive deflection was calibrated in mmHg s⁻¹ using a triangular-wave signal of known slope. Intermittent measurements were made of arterial, coronary sinus (CS), and GCV oxygen saturations and lactate concentrations. Lactate was analyzed by a direct microfluorometric assay with lactic dehydrogenase in an NAD-to-NADH linked reaction. A calibrated hemoximeter (Radiometer SM-2) measured oxygen saturations. Measurements were made of $P_{O_2}$, $P_{CO_2}$ and pH from the same blood samples. Oxygen content was calculated by adding dissolved oxygen (0.003 ml·mmHg⁻¹·dl⁻¹) to oxygen combined with hemoglobin (1.34·Hb%·Sat Hb). We measured myocardial blood flow with radioactive microspheres (mean diameter ± SD, 9 ± 1 μm or 15 ± 1 μm; 3-M Company, St. Paul, Minnesota). The microspheres were labeled with $^{125}$I, $^{153}$Gd, $^{57}$Co, $^{51}$Cr, $^{113}$Sn, $^{85}$Sr, $^{99}$mNb, or $^{46}$Sc and were prepared as described in an earlier report. We injected 1.8 × 10⁶ to 2.2 × 10⁶ microspheres into the left atrium over a 30-s period and simultaneously withdrew about 12 ml blood from the central aorta over a 2-min period for a reference sample. The exact reference flow was calculated gravimetrically, by withdrawing blood into four vials of known weights.

**Surgery**

We performed a left thoracotomy and removed the fourth rib. The pericardium was opened, and catheters were inserted in the coronary sinus, left atrium, and the aortic arch. The proximal left-anterior descending coronary artery (LADCA) and its companion, the great cardiac vein (GCV), were dissected from their fibro-alveolar covering. A calibrated flow transducer (Howell Instruments), and distal to it, a lightweight 3-mm adjustable plastic stenosis device, were placed adjacent to each other on a portion of the LADCA 2 – 6 cm from
At the end of each experiment, the dog was killed by a large dose of sodium pentobarbital. We removed, weighed, and selectively perfused the heart with three different dye-colored dextran solutions, using the method described by Reimer and Jennings.12 The left coronary ostium was sewn shut, and catheters were inserted into the LADCA proximal to the stenosis, distal to the stenosis, and into the right coronary ostium. At a perfusion pressure of 90 mmHg, three dyes simultaneously perfused the heart through the three catheters. These three colors defined the amount of myocardium perfused by the right coronary artery, by the LADCA distal to the stenosis, and by the circumflex artery and the LADCA proximal to the stenosis. After fixation in formalin for 4–7 days, the left ventricle was removed and cut into 10–12 horizontal sections parallel to the arteriovenous (a-v) groove. Two dye colors appeared in the left ventricle, one representing perfusion of the area distal to the LADCA stenosis and one representing perfusion of the area proximal to the stenosis and the circumflex artery. The right coronary artery afforded little or no perfusion to the left ventricle. A representative section of the middle portion of the heart is shown in figure 2.

The area of myocardium where the two colors met constituted less than 5% of the left ventricle and was not included in any of the measurements of regional flow. Areas perfused by different vessels were separated (fig. 2, heavy dotted lines), and each area then was divided transmurally into thirds.

The radioactivity of the blood samples obtained during injection of the microspheres and the myocardial tissue samples were counted in a well scintillation counter with a sodium iodide (TI) crystal (Searle Analytic, Inc.) connected to a 512-channel pulse-height analyzer. The stripping method of Heymann et al.11 was used to determine the total activity of each nuclide. We calculated the total regional blood flows in the heart (ml·min⁻¹) as the flow for the reference blood sample (ml·min⁻¹) multiplied by the ratio of counts per minute in the heart to the counts per minute in the reference sample. Cardiac output (l·min⁻¹) was calculated as the flow for the reference sample (l·min⁻¹) multiplied by the ratio of total counts per minute injected into the left atrium to the counts per minute in the reference sample. Transmural subendocardial/subepicardial flow ratios (I/O) were obtained by comparing flow (ml·min⁻¹·g⁻¹) from the third of the left ventricle closest to the endocardium with that of the third closest to the epicardium. We then calculated total regional flows and I/O flow ratios for the portion of the myocardium perfused distal to the stenosis. This portion of the myocardium will be called the "stenotic" left ventricle. We also calculated the total regional flows and I/O flow ratios for the area of the left ventricle perfused by nonstenotic arteries. This portion of the myocardium will be called "normal" myocardium.

**Experimental Protocol**

Continuous measurements were made of pressure in the central aorta, left ventricle, coronary sinus, left atrium, and the distal LADCA. LADCA phasic and mean flow and transmural ECG also were measured. We measured cardiac output; regional myocardial blood flow; and arterial, GCV, and coronary-sinus lactate concentrations, and oxygen tensions and saturations at the following intervals: 1) 45–60 min after completing the surgical procedure and adjustment of the halothane concentration (the control period); 2) after 30 min of coronary stenosis; and 3) after 60 min of deliberate hypotension (mean systemic blood pressure, 50 mmHg). Hypotension was induced by administering sodium nitroprusside (SNP), trimethaphan, or high concentrations of halothane. Selection of the technique was random.

Two degrees of stenosis were studied. The lesser stenosis (termed "critical" in the literature and hereafter identified as such) is one that changes resting coronary

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**LADCA (distal to stenosis)**

![Diagram of LADCA](image)

**Circumflex + Proximal LADCA**

Fig. 2. Section from the middle third of the left ventricle. A small cap of right ventricle is seen on the right. Supplied area is area dye by perfusion distal to the stenosis on the left-anterior descending coronary artery (LADCA). Horizontal sections are totalled for the left ventricle by layer and by coronary artery distribution.

Data were analyzed to determine the effects of various factors that vary with the degree of stenosis (two levels) in each subject included in the experiment. Two levels of stenosis (normal, after stenosis) were studied, and the response to stenosis was determined. The LADCA flow only slightly increased (50% increase) in response to lactic acidosis and the flow increased after stenosis. Hypotension was induced for 60 min of stability, and the response was tested for statistical significance.
CORONARY ARTERY STENOSIS AND HYPOTENSION

Table 1. Hemodynamic Effects (Mean ± SE) of Three Techniques of Inducing Hypotension

<table>
<thead>
<tr>
<th>Technique</th>
<th>Systemic Blood Pressure (mmHg)</th>
<th>Heart Rate (beats/min⁻¹)</th>
<th>Cardiac Output (l/min⁻¹)</th>
<th>Systemic Vascular Resistance (dyn·s·cm⁻⁵)</th>
<th>LV dP/dt (mmHg·min⁻¹)</th>
<th>Maximal Positive LV dP/dt (ml·100 g⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control* (n = 18)</td>
<td>92 ± 3</td>
<td>116 ± 5</td>
<td>3.58 ± 0.30</td>
<td>2,217 ± 159</td>
<td>4.8 ± 0.8</td>
<td>1462 ± 59</td>
</tr>
<tr>
<td>Hypotension and stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.91 ± 1.86</td>
</tr>
<tr>
<td>3% methanephal (n = 6)</td>
<td>51 ± 1</td>
<td>101 ± 8T</td>
<td>2.40 ± 0.19</td>
<td>1,949 ± 145+</td>
<td>0.2 ± 2.0</td>
<td>994 ± 64</td>
</tr>
<tr>
<td>Halothane (n = 6)</td>
<td>49 ± 2</td>
<td>109 ± 4+</td>
<td>1.42 ± 0.092$</td>
<td>2,656 ± 160‡</td>
<td>5.1 ± 1.7‡</td>
<td>562 ± 47‡</td>
</tr>
<tr>
<td>Sodium nitroprusside (n = 6)</td>
<td>49 ± 1</td>
<td>132 ± 7</td>
<td>3.70 ± 0.41</td>
<td>1,088 ± 130§</td>
<td>-1.3 ± 0.8</td>
<td>967 ± 46</td>
</tr>
</tbody>
</table>

Different from sodium nitroprusside: *P < 0.05; †P < 0.01.
Different from trimethaphan: $P < 0.05; §P < 0.01.
LVEDP = left ventricular end-diastolic pressure; MV, = myocardial oxygen consumption.
* Control values are those obtained after completion of surgery but before induction of stenosis. The hemodynamic variables during stenosis were not different from control values and are not presented. Control values are means across all animals, regardless of the drug used to produce hypotension.

flow only slightly but abolishes the hyperemic response produced by 10 s of complete occlusion of the coronary artery. The second level of stenosis (hereafter called "severe") reduced resting coronary artery blood flow by 40%. We induced critical stenosis in nine dogs, and severe stenosis in the other nine. To induce critical stenosis we first demonstrated that the unobstructed LADCA had a normal 2–3 fold increase in flow in response to 10 s of total occlusion. After return of LADCA flow to resting levels, stenosis was induced until LADCA flow was just below resting values (5–10%). After stabilization of LADCA flow for 4–5 min, the coronary artery was occluded totally proximal to the stenosis for 10 s, and, if the reactive hyperemic response was absent or increased by less than 10% of resting LADCA flow, this stenosis was accepted. After 10–15 min of stability of LADCA flow, the reactive hyperemic response was tested again to verify the level of stenosis. To induce the more "severe" stenosis, the stenosis device was applied slowly until resting LADCA was reduced by about 40%.

Statistical Analysis

Data were analyzed using a split-plot, repeated-measures analysis of variance (ANOVA) procedure. The factors that varied between subjects were severity of stenosis (two levels) and the type of hypotensive agent administered (three drugs). The factors that varied for each subject included time of measurement (before stenosis, after stenosis but before hypotension, and after hypotension) and location of measurement (stenotic vs. normal side) for regional flows and lactate and oxygen extraction. The repeated-measures design removed between-animal differences in the mean level of hemodynamic variables, enabling us to assess the effects of stenosis and hypotension within animals. For each dependent variable, a separate split-plot ANOVA was performed. Tests for appropriateness of the statistical model (homogeneity and symmetry of the covariance matrices) were performed and met for all analyses. We used an analogue of Fisher's protected t test to protect against spurious significance in comparing between-individual means. Only when an overall test was significant within the split-plot ANOVA (e.g., time of measurement × type of hypotensive agent) did we proceed to perform t test analysis on individual means. Matched paired t tests were used for within-subject effects; independent sample t tests were used for between-subject tests. Data are reported as means ± SE of the mean.

Results

The mean weight (±SE) of the left ventricle of the 18 dogs was 111.6 ± 5.5 g. Dye perfusion studies indicated that the mean percentage (±SE) of the weight of the left ventricle distal to the LADCA stenosis was 23.3 ± 1.9.

The production of either degree of coronary artery stenosis had no effect on PaCO₂, pH, or arterial oxygen-hemoglobin saturation. Control values were PaCO₂ = 37.4 ± 1.1 mmHg, pH = 7.38 ± 0.01, and arterial oxygen-hemoglobin saturation = 99.5 ± 0.2%. The combination of coronary artery stenosis and deliberate hypotension resulted in a significant decrease in pH (from 7.36 ± 0.01 to 7.34 ± 0.02) and arterial oxygen-hemoglobin saturation (from 99.5 ± 0.2% to 96.8 ± 1.0% (P < 0.05) when values for all animals were combined. There was no difference in acid-base or arterial oxygenation between the different techniques used to produce deliberate hypotension.

General Hemodynamics

Stenosis of the coronary artery did not change mean systemic blood pressure, heart rate, cardiac output, sys-
temic vascular resistance, left ventricular end-diastolic pressure, maximum positive LV dP/dt, or MV\textsubscript{O\textsubscript{2}}. Only when hypotension was superimposed on stenosis did these variables change. Data for these control hemodynamic variables and the effect of stenosis with deliberate hypotension are shown in table 1. Mean systemic blood pressures were similar for all three techniques of inducing hypotension. As expected, the mechanism by which blood pressure was reduced differed among the drugs used to produce hypotension. In comparison to sodium nitroprusside and trimethaphan, halothane reduced cardiac output without changing systemic vascular resistance. Trimethaphan was intermediate between halothane and sodium nitroprusside in its effect on these variables. Heart rate was least during trimethaphan and greatest with sodium nitroprusside. LVEDP was greatest during hypotension with halothane. Left ventricular dP/dt, which was reduced by all hypotensive techniques, was lowest with halothane. MV\textsubscript{O\textsubscript{2}} was reduced to 83%, 65%, and 45% of each group's control value by sodium nitroprusside, trimethaphan, and halothane, respectively.

**EFFECT OF STENOSIS AND HYPOTENSION ON CORONARY BLOOD FLOW**

The effects of stenosis and hypotension on coronary blood flow (LADCA), regional myocardial flow, I/O ratios, and coronary artery perfusion pressure (CAPP, coronary artery diastolic pressure minus LVEDP) are presented in table 2. Critical stenosis with hypotension and severe stenosis (both with and without hypotension) reduced flow of the LADCA. Comparison between the stenotic and normal heart revealed that the combination of hypotension and critical stenosis reduced subendocardial blood flow but did not change epicardial flows or I/O ratios. Severe stenosis without hypotension reduced subendocardial flow in the ischemic as compared to the normal myocardium with no significant change in subepicardial flow or I/O flow ratios. With hypotension, severe stenosis reduced subendocardial and subepicardial flows and I/O flow ratios. Stenosis resulted in a reduction in CAPP when compared with measurements made in the normal arterial tree. During hypotension, critical and severe stenosis resulted in CAPP of 27 ± 3 and 17 ± 2 mmHg, respectively.

**MYOCARDIAL LACTATE AND OXYGEN EXTRACTION**

Venous blood from the GCV and the coronary sinus produced similar values for lactate extraction and arteriovenous oxygen content difference during the control period and during both degrees of stenosis (table 3). Lactate extraction in the CS was greater during critical stenosis then during critical stenosis plus hypoten-
CORONARY ARTERY STENOSIS AND HYPOTENSION

TABLE 3. Myocardial Lactate and Oxygen Extraction in the Coronary Sinus (CS) and Great Cardiac Vein (GCV) during Moderate and Severe Stenosis with and without Hypotension

<table>
<thead>
<tr>
<th></th>
<th>Lactate Extraction (%)</th>
<th>Arterial-Venous Oxygen Difference (ml/dl⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>GCV</td>
</tr>
<tr>
<td>Critical stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>33 ± 7</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>Without hypotension</td>
<td>42 ± 7</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>With hypotension</td>
<td>27 ± 5</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>26 ± 5</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>Without hypotension</td>
<td>30 ± 6</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>With hypotension</td>
<td>17 ± 6</td>
<td>-8 ± 11</td>
</tr>
</tbody>
</table>

Values are mean ± SE.
Different from CS: *P < 0.05.
Different from moderate stenosis: †P < 0.01.
Different from stenosis without hypotension: ‡P < 0.05; §P < 0.01.
Different from control: ‡P < 0.05; **P < 0.01.

Severe stenosis plus hypotension decreased lactate extraction in coronary sinus blood samples, and to a greater degree, in GCV blood samples. Five of nine animals with severe stenosis and hypotension had evidence of net lactate production in blood samples from the GCV; no animal had net lactate production in samples from the coronary sinus. Evidence of increased arterial-venous oxygen content difference was present in blood samples from the GCV during severe stenosis and hypotension.

EFFECTS OF HYPOTENSIVE DRUGS

The effects of the three drugs on regional myocardial blood flow and oxygen consumption in the normal heart are presented in table 4. Trimethaphan and halothane significantly reduced subendocardial and subepicardial blood flow with no change in I/O ratio. A similar percentage reduction in MV0₂ occurred for each agent. Sodium nitroprusside did not affect significantly regional coronary artery blood flow or MV0₂ but did reduce the I/O ratio.

EFFECTS OF HYPOTENSIVE DRUGS DURING STENOSIS

The subendocardial blood flow and I/O flow ratio were reduced in the ischemic myocardium compared with the normal myocardium during hypotension with severe stenosis (P < 0.01 for both variables) but not critical stenosis. The combined effect of severe stenosis and hypotension on subendocardial blood flow, I/O ratio, net lactate extraction, and CAPP are presented for each drug in table 5.

ELECTROCARDIOGRAPHIC RESULTS

Insertion of wire electrodes in the myocardium resulted in a change in ST segment that returned towards baseline with time. The initial mean (±SE) depression of ST segment for all animals in the control condition was 1.08 ± 0.5 mV. Critical stenosis, with or without hypotension, failed to increase depression of the ST segment (mean values of 0.89 mV and 0.94 mV, respectively). In contrast, the more severe stenosis, with or without hypotension, significantly decreased ST segments; mean values (±SE) were 2.22 ± 0.99 mV (P < 0.05) and 2.88 ± 1.17 mV (P < 0.01), respectively.

DISCUSSION

We believe our canine model of coronary artery stenosis is appropriate for studying the effects of intra-operative interventions, e.g., deliberate hypotension. Our control measurements were obtained during both

TABLE 4. Effects of Hypotension on Regional Myocardial Blood Flow and Oxygen Consumption (MV0₂) in the Normal Heart

<table>
<thead>
<tr>
<th></th>
<th>1 ml·g⁻¹</th>
<th>O ml·g⁻¹</th>
<th>I/O</th>
<th>MV0₂ (ml·100 g⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.92 ± 0.10</td>
<td>0.84 ± 0.10</td>
<td>1.08 ± 0.05</td>
<td>7.91 ± 0.69</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethaphan</td>
<td>0.92 ± 0.10</td>
<td>0.84 ± 0.10</td>
<td>1.08 ± 0.05</td>
<td>7.91 ± 0.69</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.92 ± 0.10</td>
<td>0.84 ± 0.10</td>
<td>1.08 ± 0.05</td>
<td>7.91 ± 0.69</td>
</tr>
<tr>
<td>Sodium Nitroprusside</td>
<td>0.92 ± 0.10</td>
<td>0.84 ± 0.10</td>
<td>1.08 ± 0.05</td>
<td>7.91 ± 0.69</td>
</tr>
</tbody>
</table>

* A value significantly less than control (P < 0.05).

Control values are those obtained for all the animals and did not differ between groups. The effect of the hypotensive drugs on regional blood flow and MV0₂ are reported in percentages of each group's own control.

1 = subendocardial blood flow; O = subepicardial blood flow.
anesthesia and surgical stimulation. The simultaneous occurrences of these two conditions simulates the clinical situation in which patients are anesthetized and undergoing surgery before induction of hypotension. The degree of stenosis induced is one of the major variables in the design of this study. We wanted to produce a model of the clinical situation that frequently exists during anesthesia and surgery in patients with ischemic heart disease: coronary reserve is compromised, but, given the absence of additional problems (i.e., hypertension, hypotension, blood loss, fluid overload, hypoxemia, or arrhythmias), myocardial ischemia does not occur.

To accomplish this, we studied a degree of stenosis that is termed "critical" in the literature. Critical stenosis is defined as the minimum constriction sufficient to prevent an increase in coronary blood flow over resting values in response to increased myocardial oxygen demands. This loss of vasodilatory capacity indicates that coronary vascular reserve has been exhausted. Resting coronary blood flow should be affected little by critical stenosis. Gould et al. reported in experimental studies on dogs that with critical stenosis resting coronary blood flow changed only slightly and coronary artery diameter was reduced from 88-93%. Elzinga and Skinner, in similar dog studies, reported that critical stenosis decreased resting coronary blood flow and coronary artery diameter by 19% and 75%, respectively. These two investigator's results, while similar, have slight differences that may be secondary to different methods for measurement of stenosis and/or employment of different anesthetics. In any event, in patients with ischemic heart disease, angiographers consider a stenosis of 70% to represent a hemodynamically significant stenosis that is appropriate to correct surgically. In our study, critical stenosis resulted in a reduction of resting coronary blood flow of 9% (table 2). The loss of vasodilatory capacity indicates that coronary vascular reserve has been exhausted. The combination of critical stenosis and deliberate hypotension reduced the coronary artery pressure and the subendocardial myocardial blood flow in the stenotic side when compared with the normal side. LADCA perfusion pressure was reduced to a mean value of 27 mmHg. Despite this, no signs of ischemia were seen, i.e., net lactate production, redistribution of regional blood flow, or change in ST segments.

In the second part of this study, we wished to test the ability of our model to identify the occurrences of myocardial ischemia when severe stenosis was present and ischemia very likely to occur. To accomplish this we induced a stenosis that reduced coronary blood flow by 40%. Studies in dogs suggest that when coronary blood flow is reduced to this extent, signs of myocardial ischemia may occur. Scheuer and Brachfeld reported the reducing coronary blood flow approximately 50% resulted in depression of the ST segment, excess lactate, or atrial hypertension. Wegría and co-workers noted minimal and then marked changes in ST segments when coronary blood flow was reduced by 29% and 52%, respectively. In these two studies, dogs were anesthetized with pentobarbital. Similarly, in dogs anesthetized with alpha choralose, Waters and co-workers found biochemical and mechanical evidence of myocardial ischemia when coronary blood flow was reduced by 52%. In our study, the effect of a stenosis that reduced CBF by 40% produced ECG signs of myocardial ischemia. This ischemia was not confirmed by either a decrease in net lactate extraction or a redistribution of CBF. Direct implantation of electrodes in the subendocardium may have enabled us to detect myocardial ischemia earlier by ECG monitoring. Nevertheless, we were surprised that we could not confirm this ischemia by direct flow measurements or measurement of lactate extraction. With the imposition of deliberate hypotension, all of these animals had signs of myocardial ischemia, as evidenced by greater ST segment changes, production of lactate, and redistribution of CBF.

How we quantitated the degree of stenosis, the amount of myocardium affected, and the method of determination of stenosis are clearly dependent. We used physiologic methods for measurement of stenosis. These criteria were based on the assumption that coronary angioscopy, LADCA flow by flow cytometry, and the amount of myocardial ischemia that occurs is dependent on the degree of stenosis. The amount of myocardial ischemia was,
production of stenosis are of major importance in this study. We used physiologic criteria to define the amount of stenosis. These criteria included continuous measurement of coronary artery pressure distal to the stenosis, LADCA flow by flowmeter, and regional flow by microspheres. The amount of the left ventricle distal to the stenosis was defined by dye perfusion. Additional definition of the degree of stenosis using other criteria, such as angiography, and a method for continuous measurement of the size of the stenosis would have been desirable. However, the measurement of the degree of stenosis by angiography has limitations, and we do not know of any method of continuously measuring the size of a stenosis.

Two recent studies examining the effects of anesthetics on the myocardium in the presence of a coronary stenosis illustrate the importance of measuring and defining the degree of stenosis imposed. Lowenstein and co-workers produced a coronary artery stenosis using a mechanically driven snare. They defined the degree of stenosis as critical when a combination of stenosis and arterial hypoxemia produced regional myocardial dysfunction distal to the stenosis. These investigators then demonstrated that in the presence of normoxemia and a stenotic coronary artery, increasing the concentration of halothane produces evidence of myocardial ischemia, i.e., regional myocardial dysfunction distal to the stenosis. The highest concentration of halothane used by these workers reduced mean systemic blood pressure to approximately 50 mmHg, a value similar to that obtained in this study. We also found evidence of regional myocardial ischemia, although by indices different than those employed by Lowenstein’s group. Comparing our work with Lowenstein’s requires a method of measuring and defining the degree of stenosis. In another study, Merin et al. examined the effects of two anesthetic regimens (nitrous oxide with fentanyl or with halothane) on the production of myocardial ischemia by reducing CBF 60%. The amount of myocardial ischemia produced did not differ between the two anesthetics. However, coronary blood flow and indices of myocardial supply and demand did differ. The imposition of a stenosis that reduced CBF by 60% may well have resulted in a different degree of stenosis being induced in the animals anesthetized with fentanyl than with halothane. Thus, that study not only examined differences between anesthetic drugs but also possibly differing degrees of stenosis. Again, a method for quantitating the degree of stenosis imposed would be desirable.

Another factor to consider is how the stenosis is produced. An externally applied stenosis produced by a rigid clamp may impose different changes in stenosis resistance than those found in coronary artery stenosis in man. Indeed, in a postmortem study of coronary artery stenosis in man, Logan reported two types of stenoses that respond differently to changes in systemic pressure.

In this study, induction of stenosis did not produce evidence of left ventricular dysfunction, i.e., changes in stroke volume, LVEDP, or maximum positive LV dp/dt. It was not surprising to us that we found no evidence of left ventricular dysfunction during critical stenosis, as CBF was not decreased. However, during severe stenosis, when CBF was reduced 40%, we also found no evidence of left ventricular dysfunction at control aortic pressures. This finding conflicts with results reported by Merin et al. The difference could be secondary to differences in species and experimental design. Merin studied piglets and reduced CBF by 60%, whereas we studied dogs and reduced CBF by 40%. Additionally, in our study, dye perfusion of the coronary arterial tree indicates that less than 25% of the left ventricle muscle mass was distal to the stenosis. Perhaps a greater percentage of ventricular muscle involvement is necessary for left ventricular dysfunction to be discernible by the measurements we used.

Although lactate metabolism is a sensitive indicator of myocardial ischemia, it can present difficulties in interpretation. Normally the myocardium extracts lactate. A decrease in this extraction, or the production of lactate, indicates anaerobic metabolism and myocardial ischemia. Although a decrease in lactate extraction to 10% or less has been considered an indication of myocardial ischemia, recent work by Gertz et al. cast doubt on this assumption. These investigators found that lactate extraction of less than 10% could occur in healthy young men during fasting, and they concluded that an absolute value for lactate extraction could not be used to indicate myocardial ischemia. They suggested that only the production of lactate could be used as a certain sign of abnormal myocardial metabolism.

Opie and co-workers and, more recently, Roberts et al. examined the problems in using measurements of lactate production from coronary sinus blood to document regional myocardial ischemia. Opie and coworkers measured lactate concentration after ligating a coronary artery in dogs. Lactate concentration was two to four times greater in ischemic tissues than in venous blood from ischemic tissue, and eight to 16 times greater in ischemic tissue than in blood from the coronary sinus. Roberts et al. compared lactate extraction in blood samples from the GCV and coronary sinus before and after ligation of the LADCA. In 15 of 17 animals, net lactate extraction was less in blood samples from the GCV than in those from the coronary sinus. However, net lactate extraction in the GVC was 10% or less in...
only 10 of these animals. These studies illustrate the problem of using venous blood samples to document regional tissue ischemia. This is particularly applicable to the myocardium, because ischemia may be limited to the endocardium.28 Another concern is the possibility of venous cross-circulation. Work by Nakazama et al.29 indicates that the GCV receives less than 5% of the flow from the circumflex artery. Thus, it is appropriate to sample the GCV to study LADCA-induced stenosis.

The use of radioactive microspheres to measure regional myocardial blood flow helps to determine the occurrence of myocardial ischemia. Becker et al.30 used radioactive microspheres to determine regional flow 30–60 min after acute occlusion of the coronary artery. Reduction in blood flow was greatest in both the endocardium and in the center of the occluded area. I/O flow ratios were below 0.4 in areas where flow was reduced by more than 50%. Smith and co-workers31 found similar results. However, these studies and ours differ in experimental conditions. Both Becker and Smith examined changes in flow secondary to coronary artery occlusion; except for the effect of the occlusion, MVO₂ presumably would remain constant. In our study, deliberate hypotension may reduce MVO₂. Also, some of the drugs used to produce hypotension directly affect coronary blood flow, making comparison between the stenotic and the normal heart (and interpretation of the resulting data) difficult.

In this study we implanted subendocardial electrodes to obtain the most sensitive site for the diagnosis of ischemia. Barnard and co-workers32 demonstrated that transmural placement of electrocardiographic leads across the wall of the left ventricle provided a more sensitive measure of subendocardial ischemia than did a standard transthoracic electrocardiogram. Similarly, Battler et al.33 demonstrated greater sensitivity in the detection of subendocardial ischemia by recording from the subendocardium than from the chest surface.

Recent work by Vatner34 in awake dogs demonstrates a good correlation between reduction in CBF and regional endocardial function (ultrasonic dimension technique). A reduction of CBF of 10–20% resulted in impaired subendocardial function. This work indicates measurement of regional myocardial function could provide a sensitive index of myocardial ischemia and perhaps the method should have been employed in this study. However, in open-chested anesthetized dogs, earlier studies by several investigators required a much greater reduction in CBF before consistently reduced regional function could be seen.18,35,36 Thus, the sensitivity of this measurement, at least in anesthetized animals, is open to question.

To gain as much information as possible about the usefulness of this animal model, we used three contrasting methods of inducing hypotension. The degree of stenosis and hypotension being equal, one might assume that the hypotensive technique of choice would be that producing the most favorable hemodynamic index of myocardial oxygen supply and demand. We believe that this approach would be too simplistic, because hypotensive drugs also may affect regional distribution of coronary blood flow. Administration of sodium nitroprusside has been shown to result in uneven distribution of coronary blood flow distal to a stenotic or occluded coronary artery in both animals37 and humans.38 In contrast, cervical epidural block in the dog resulted in favorable distribution of coronary blood flow distal to an occluded coronary artery.39 This finding was attributed to elimination of adrenergic tone by sympathectomy produced by the epidural block. Earlier studies in the dog support this thesis by demonstrating that cardiac denervation reduced the size of myocardial infarction.40 Perhaps, then, ganglionic blockade by trimethylamine nitrate might be beneficial.

At relatively low doses, halothane has been demonstrated to reduce an electrocardiographic index of myocardial ischemia in animals41 and to provide greater coronary vascular reserve.42 Halothane also has been shown to reduce MVO₂ in a dose-related fashion.43,44 Perhaps a high concentration of halothane, such as that used to induce hypotension, might have an even more favorable effect. Despite these theoretic considerations, the degree of stenosis was of greater importance than the technique selected to produce hypotension. In our preparation with a critical stenosis, the induction of hypotension proved innocuous to the myocardium. However, the three techniques of inducing hypotension affected regional myocardial blood flow and I/O flow ratios differently. In the normal section of the heart, trimethylamine and halothane reduced both subendocardial and subepicardial blood flows, while I/O flow ratios were maintained. In contrast, myocardial flow was maintained with the administration of sodium nitroprusside while I/O ratio decreased. This decrease in I/O flow ratios resulted from an increase in flow to the subendocardium, while at the same time MVO₂ decreased. We believe the increase in flow resulted from the vasodilatory action of sodium nitroprusside, an effect that would occur throughout the myocardium. The increase in flow is less, or does not occur, in the subendocardium because flow is impeded during systole.45

The combination of critical stenosis and hypotension did not produce any evidence of myocardial ischemia using our criteria for detecting ischemia. Severe stenosis without hypotension did produce electrocardiographic evidence of subendocardial ischemia, but significant decrease in flow is less, or does not occur, in the subendocardium because flow is impeded during systole.45

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evidence of subendocardial ischemia and a concomitant small but significant reduction in subendocardial flow when the stenotic and normal sides were compared. Blood flow was not redistributed, nor net lactate extraction affected. If we had used a more sensitive indicator of ischemia, such as transmural tissue biopsy and subendocardial analysis for lactate concentration, we might have found biochemical evidence of ischemia.

When stenotic and normal areas of the left ventricle were compared, the addition of hypotension to severe stenosis produced evidence of ischemia, i.e., production of lactate or a decrease in lactate extraction, a reduction in coronary blood flow, a reduction in I/O flow ratio, or changes in ECG (tables 2, 3). Our study is not designed to provide comparative data concerning which of the hypotensive drugs might be preferable to use to induce hypotension in the presence of coronary artery stenosis. There is a suggestion that trimethaphan may have some advantages (table 5), and we believe this warrants further study. Although many differences exist between an animal model of single vessel acute coronary artery stenosis and the patient with chronic multivessel coronary artery disease, this study suggests deliberate hypotension should be tolerated well in a asymptomatic patient with coronary artery disease. However, in a cautionary vein, the small change in coronary artery perfusion pressure (27 to 17 mmHg) required to induce myocardial ischemia by all the criteria employed in this study indicate the importance of small changes in diameter of stenosis, diastolic blood pressure, and cardiac filling pressures that could reduce CAPP and induce myocardial ischemia.

This study describes a canine model of acute coronary stenosis for the study of intraoperative interventions. In the presence of critical stenosis, deliberate drug-induced hypotension to 50 mmHg resulted in a CAPP of 27 mmHg but failed to show any evidence of myocardial ischemia. In the presence of a more severe stenosis, deliberate hypotension reduced CAPP to 17 mmHg and produced myocardial ischemia. In any evaluation of the possible myocardial hazard of deliberate hypotension, the severity of disease, i.e., the degree of stenosis, is of paramount importance.

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Clinical

Mucluual

A. A. d'HOLLA

The effects of age on some steroidal muscle relaxants—d-tubocurarine—have been dramatically, the plasma fraction decreases by aging.1,2 As measured with the open-systole, elderly patients may be at risk for excessive muscle relaxation, while young patients may require increased dosage for adequate muscle relaxation.3

Recently, a new muscle relaxant, besylate, which enhances the physiologic pH and the elimination pathways, has been presented for clinical evaluation.2,4 However, the elimination pathways are not well controlled and this may result in decreased muscle relaxation and hyperemic effect.5,6 It is possible7 that, to a great extent, the elderly population will not be controlled by the elimination pathways. However, age-related changes in muscle function, which are implicated in eliminating the drug, may greatly affect the elderly population.

The aim of this study was to investigate the effects of age on muscle relaxant metabolism. We studied a group of human subjects, T1,6,7 and the lack of marked differences was noted. We also made it possible to study muscle relaxant metabolism.8-10 The influence of muscle relaxant metabolism on the elderly population will be studied after obtaining

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