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Greater Coronary Vascular Reserve in Dogs Anesthetized with Halothane

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To compare the effects of two dissimilar anesthetic regimens on hemodynamic factors affecting the risk of myocardial ischemia, the authors recorded myocardial blood flow as an indicator of oxygen supply during autoregulation and maximal vasodilatation at various coronary arterial perfusion pressures while myocardial oxygen demand was stable, and used the relationship between pressure and blood flow as an index of coronary vascular reserve. Pressure–flow relations in the left circumflex coronary artery during light halothane–oxygen–relaxant anesthesia and during nitrous oxide–oxygen–relaxant anesthesia were compared in 11 dogs. Changes in coronary arterial pressure were induced by hydraulic constriction and recorded through a small catheter in the circumflex coronary artery for each anesthetic regimen during autoregulated and during maximally vasodilated coronary arterial blood flows. Flow was measured by an electromagnetic flow transducer on the circumflex coronary artery and by radioactive microspheres.

There were two major differences between the two anesthetic regimens. First, myocardial oxygen demand was less during halothane anesthesia, as measured by myocardial oxygen consumption, wall tension, or the rate–pressure product. Myocardial blood supply decreased similarly during halothane anesthesia. Second, with halothane anesthesia the pressure–flow relationship during maximal vasodilatation was significantly shifted to the left. This parallel shift to the left reflects the lower coronary arterial perfusion pressure at which flow becomes zero, and is best explained by the vascular waterfall theory. Based on this theory, minimal coronary vascular resistances are similar with the two anesthetic regimens, since the maximal vasodilatation lines are parallel, but diastolic intramyocardial tissue pressure is probably lower with halothane, accounting for the lower coronary arterial diastolic pressure at which flow stops. In addition, this shift also reflects the lower coronary arterial perfusion pressure at which subendocardial ischemia occurs when autoregulation of blood flow is present. Therefore, dogs lightly anesthetized with halothane have greater coronary vascular reserves than do dogs anesthetized with nitrous oxide. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Heart: blood flow, myocardial; coronary vascular reserve; coronary vascular resistance; myocardial function; myocardial oxygen consumption.)

CONTROVERSY EXISTS about what anesthetic to give patients with known or suspected coronary arterial disease to minimize the risk of perioperative myocardial ischemia or infarction.[1–4] In particular, halothane has been thought either dangerous because it lowers perfusion pressure or beneficial because it lessens myocardial oxygen demand. One randomized prospective clinical trial showed by electrocardiographic criteria less myocardial ischemia in patients anesthetized with halothane than in those anesthetized with morphine and other agents.[5] Another clinical trial demonstrated that depressed ST-segments on electrocardiograms often reverted to normal when halothane was added to other anesthetic regimens (Dr. G. Edelist, unpublished observation). Two experimental studies in dogs showed that the ST-segment elevation caused by total coronary arterial occlusion could be reduced during halothane anesthesia.¶[6] On the other hand, Smith *et al.*[7] found that in dogs halothane increased myocardial oxygen extraction, and therefore thought that it had jeopardized the supply–demand balance.

Only Smith *et al.*[7] measured myocardial oxygen consumption and blood flow, but in no study was the myocardial oxygen supply–demand relationship examined quantitatively when myocardial oxygen demand was increased or myocardial oxygen supply was decreased to determine how each component was affected by the anesthetic chosen. Therefore, this study was designed to measure myocardial oxygen demand, myocardial oxygen supply, and their balances at various coronary arterial perfusion pressures in dogs anesthetized with two different anesthetic regimens. A nitrous oxide–oxygen–relaxant regimen was chosen to illustrate what happens when coronary arterial perfusion pressure, heart rate, myocardial oxygen demand, and myocardial blood flow are maintained or increased. A halothane–oxygen–relaxant regimen was chosen as the prototype of what happens when myocardial oxy-

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¶ Gerson JI, Hickey RF, Bainton CR: Treatment of myocardial ischemia with either halothane or nitroprusside–propranolol, Abstracts of the annual meeting of the American Society of Anesthesiologists, October 1978, pp 521–522.

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gen demand is reduced but so is coronary arterial perfusion pressure.

At normal coronary arterial perfusion pressures and myocardial oxygen demands, the coronary vascular bed has the ability to autoregulate blood flow to meet oxygen demands; that is, coronary vascular resistance changes in response to changes in perfusion pressure in order to maintain flow. If, during autoregulation, at any given level of cardiac work and coronary arterial perfusion pressure, the coronary vessels are maximally dilated by an infused drug, flow will increase to above its autoregulated level and become maximal; the difference between autoregulated and maximal flows is the coronary vascular reserve. If coronary perfusion pressure is lowered progressively while cardiac work and oxygen demand remain constant, the autoregulated flow at first does not change, but the coronary vascular reserve diminishes. Eventually, a point is reached when coronary vasodilatation is maximal and coronary vascular reserve is zero. Any further reduction of pressure will now decrease resting coronary arterial blood flow. In this study we hoped to find out whether, with the two anesthetic regimens, autoregulation became exhausted at different pressures, and whether the extents of coronary vascular reserve at normal and low perfusion pressures differed.

Methods and Materials

Surgical Preparation

Subjects of the study were 11 mongrel dogs weighing 28–35 kg each. We induced anesthesia with sodium thiopental (25.0 $mg \cdot kg^{-1}$, iv), gave pancuronium bromide (0.1 $mg \cdot kg^{-1}$), and ventilated each dog through an endotracheal tube attached to a Harvard respirator. A mixture of nitrous oxide (75–80 per cent) and oxygen (20–25 per cent) or a mixture of halothane (0.8 per cent) and oxygen (99.2 per cent) was then delivered from a Foregger anesthesia machine. Supplemental thiopental (3.0–4.0 $mg \cdot kg^{-1}$, iv) or pancuronium bromide (0.05 $mg \cdot kg^{-1}$) was given whenever there were signs of light anesthesia, such as eyelid reflex or slight movement; these signs occurred during the surgical preparation only rarely. Halothane anesthesia was administered to maintain an end-expiratory concentration of 0.8 per cent. We allowed 20 minutes for blood–brain equilibration at constant end-expiratory concentration (measured continuously by an infrared halothane analyzer, Beckman LB-2) before recording values for any variable. This concentration of halothane in dogs nearly corresponds to the minimum alveolar concentration (MAC).

Arterial blood-gas and *p*H values were monitored frequently during the experiment. The Pa_{CO_2} was maintained between 29 and 42 torr by adjusting the ventilatory volume or rate; in any one dog Pa_{CO_2} changed no more than 3 torr throughout the study. The *p*H was maintained between 7.36 and 7.45 by correcting the base deficits with sodium bicarbonate. The Pa_{O_2} was 100 torr or more during anesthesia with both anesthetic techniques. The electrocardiogram was monitored in all experiments.

Three catheters were inserted into the femoral vessels: a stiff #8 polypropylene pigtail catheter was advanced into the left ventricle to measure left ventricular pressure (P_{LV}), the first derivative of P_{LV} (maximal positive dP/dt), and high-sensitivity left ventricular end-diastolic pressure (P_{LVED}); a stiff #8 polypropylene catheter was inserted into the aortic arch to measure central aortic pressure (P_{AO}); and a #8 polyvinyl catheter was inserted into the inferior vena cava to give intravenous fluids and drugs. Using a step-function change in pressure, we found the undamped natural frequency of the left ventricular catheter was 24–28 Hz and the damping ratio was 0.20–0.30.[8] Maximal positive dP/dt was measured by differentiating the left ventricular pressure signal with an active electronic differentiator; the positive deflection was calibrated in $torr \cdot sec^{-1}$ by a triangular-wave signal of known slope.

The pericardium was exposed through a left thoracotomy in the fourth intercostal space and opened widely parallel to the phrenic nerve. Polyvinyl catheters (#8) were inserted directly into the left atrial appendage for measuring left atrial pressure (P_{LA}) and injecting radioactive microspheres, and through the left internal mammary artery into the aortic arch for obtaining a microsphere reference sample. In six of the 11 dogs, a #5 polyethylene catheter was inserted directly into the coronary sinus for blood sampling and coronary sinus pressure (P_{CS}) measurement. The tip of this catheter was directed away from the ostium of the coronary sinus into the right atrium, and its position (approximately 2.5 cm away from the ostium) was verified at the end of the experiment. In four dogs, opposing ultrasonic piezoelectric crystals were placed on the epicardium of the left ventricle in the anteroposterior axis for continuous measurement of left ventricular diameter.[9]

The proximal left circumflex coronary artery was dissected free of its fibroareolar covering and an electromagnetic flow transducer coupled to a calibrated flowmeter (Narcomatic® RT-500) was placed near the origin of the artery (fig. 1). Distal to the flow transducer a polyvinyl hydraulic occluder was placed around the artery.[10] Finally, distal to the occluder a Silastic® pressure catheter (0.011 inch ID × 0.025 inch OD) was inserted into the artery by the Herd-Barger tech-

nique.[11] The size of this catheter was increased at the entrance into the artery by gluing the Silastic catheter into a larger polyvinyl catheter (0.030 inch ID). This pressure catheter was carefully secured in the vessel and kept free from the occluder and the flow transducer. The undamped natural frequency of this catheter system was 20–25 Hz and the damping ratio was 0.35–0.50.[8]

The flow transducer, occluder, leads from piezoelectric crystals, and all pressure catheters were brought through the pericardium via separate small stab wounds in the pericardium or via the base of the pericardiotomy incision. The pericardium then was carefully closed with minimal overlap of edges, but the chest was left open. The pressure catheters were connected to Statham P23Db pressure transducers. The electrocardiogram, phasic and mean coronary arterial blood flows, maximal positive dP/dt, and all pressures were recorded simultaneously on a Beckman 12-channel polygraph recorder.

Experimental Protocol

Our goal during each experiment was to obtain a series of pressure–flow relations in the left circumflex coronary artery by use of the electromagnetic flow transducer to measure total circumflex coronary arterial blood flow in four situations: during autoregulation and during maximal vasodilatation for both the nitrous oxide and the halothane anesthetic regimens. In addition, we obtained pressure–flow relations during autoregulation for both anesthetic regimens by use of radioactive microspheres to measure total, regional, and transmural myocardial blood flow. The microsphere-measured blood flows were used to validate the flow transducer data, to evaluate regional myocardial flows during each anesthetic regimen, and to calculate the left ventricular subendocardial/subepicardial flow ratio.

We allowed 30 minutes after completing the surgical preparation before beginning the study; at this time, heart rate and systemic pressures (P_{LV}, P_{AO}, P_{LA}, P_{CS}, P_{LVED}) were constant, and they remained so while pressure–flow relations in the circumflex coronary artery were obtained during the first anesthetic state. In seven dogs, nitrous oxide was the first anesthetic studied, and in four dogs, halothane was first.

The first series of pressure–flow relations was usually obtained with autoregulation intact. To determine the control pressure–flow relations during autoregulation, we measured pressure and flow (with the electro-magnetic flow transducer) in the unconstricted left circumflex coronary artery. We then connected the hydraulic occluder to a fluid-filled syringe

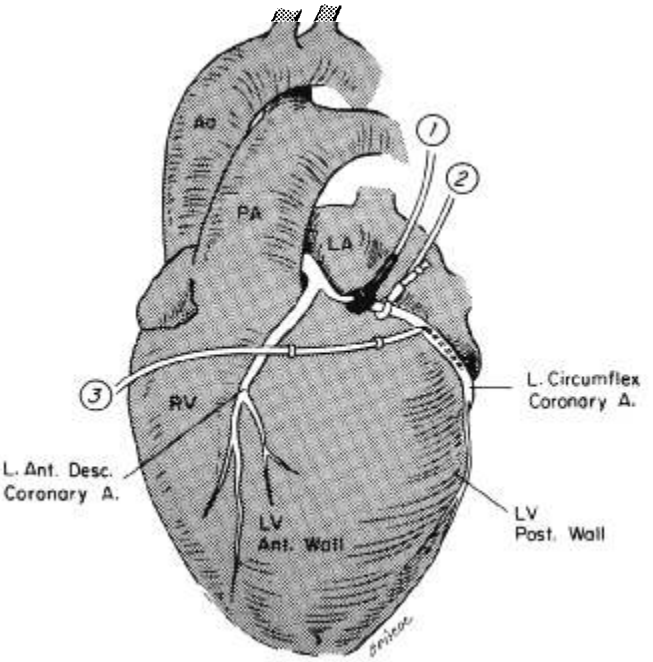

FIG. 1. Experimental preparation: 1 = electromagnetic flow transducer; 2 = polyvinyl hydraulic occluder; 3 = Silastic® (0.011 inch ID) and polyvinyl (0.030 inch ID) catheter system used to measure circumflex coronary arterial pressure.

and manually applied pressure to narrow the circumflex artery and thus lower coronary arterial pressure. At least eight serial constrictions were done in random order to achieve different coronary arterial pressures for each anesthetic state during autoregulation; the range of coronary arterial end-diastolic pressures obtained from all dogs was 20 to 120 torr. The desired pressures were usually easy to reach and to maintain for the duration of the constrictions. Once a pressure was reached, the constriction was held for 15 seconds before the pressure–flow relation was recorded; flow often decreased transiently during this time, but it quickly returned towards the control flow and stabilized. The pressure–flow relation was then recorded for analysis over a further 5–10 seconds. Release of the 20- to 25-second constriction was followed by reactive hyperemia, the magnitude of which depended on the extent of constriction. After the constriction and the subsequent reactive hyperemia, flow returned to the control value before we proceeded with the next constriction. In some experiments the constrictions were held for as long as 5 minutes, and pressure–flow relations were recorded every 30 seconds to determine whether autoregulation completely compensated for the change in pressure within 15 seconds. It did: circumflex coronary arterial blood flow did not change between 15 seconds and 5 minutes of constriction.

Once the relationship of coronary arterial pressure

and blood flow during autoregulation for the first anesthetic state was characterized from data obtained by use of the flow transducer, we were able to predict a narrow range of pressures below which the flow would decrease rapidly (the breaking point). To examine regional blood flows and their relation to the breaking point and to the autoregulatory pressure–flow relation, we measured total, regional, and transmural myocardial blood flows at three coronary arterial pressures with radioactive microspheres for that anesthetic regimen during autoregulation. The three pressures selected were control pressure (no constriction), pressure close to but above the breaking point ("medium" constriction) and pressure below the breaking point ("severe" constriction).

In a similar manner, a second series of pressure–flow measurements was then obtained for the second anesthetic regimen with the electromagnetic flow transducer and radioactive microspheres during autoregulation.

The third series of pressure–flow relations in the circumflex coronary artery was obtained during maximal coronary vasodilatation with one of the anesthetic regimens. For these measurements, we dilated the vessels by injecting carbochromen (Intensain, Hoechst-Roussel Pharmaceuticals, Inc.) into a peripheral vein. We considered coronary arterial autoregulation of blood flow to be exhausted when complete coronary arterial occlusion for 10 seconds was not followed by reactive hyperemia. The initial dose of carbochromen was given as a slow intravenous bolus (8.0 $mg \cdot kg^{-1}$); supplemental doses of 50 mg were given every 30 minutes to insure no return of reactive hyperemia. We chose carbochromen rather than adenosine since at this dose carbochromen dilates coronary arteries selectively without appreciably affecting systemic pressures or blood flow.[12]

For pressure–flow relations during maximal vasodilatation, flow was measured only by the electromagnetic flow transducer. Constrictions were done in random order from control coronary arterial pressures to coronary arterial diastolic pressures as low as 20 torr in each anesthetic state. Unlike the situation seen with constrictions during autoregulation, reactive hyperemia was not seen after release of any constriction during maximal vasodilatation. At least eight pressure–flow data points were obtained for each pressure–flow relation.

The fourth series of measurements was then obtained with the other anesthetic regimen during maximal vasodilatation.

When changing from the nitrous oxide to the halothane regimen, we allowed at least 20 minutes to pass after the end-tidal halothane concentration reached 0.8 per cent to insure blood–brain equilibration and steady-state anesthetic conditions. When changing from the halothane to the nitrous oxide regimen, we allowed 45 minutes for halothane washout and reequilibration with nitrous oxide. End-expiratory concentrations of halothane at this time were 0.1–0.2 per cent. In two experiments, the experimental protocol was reversed and pressure–flow relations during maximal vasodilatation were obtained before pressure–flow relations during autoregulation. In these experiments, we allowed at least one hour for the carbochromen effect to wear off, reactive hyperemia to return, and the autoregulation control blood flow to stabilize.

In all pressure–flow relation determinations, we plotted mean circumflex coronary arterial diastolic pressure (x axis) against mean diastolic flow (y axis) because flow to the subendocardium, which is most vulnerable to ischemia, is probably entirely diastolic.[13]

Measurement of Myocardial Oxygen Demand

Myocardial oxygen demand is the same as myocardial oxygen consumption when oxygen supply is unrestricted. In four experiments, we measured myocardial oxygen consumption by the reverse Fick equation for both anesthetic regimens during autoregulation without coronary arterial constriction. To do this, in samples of blood drawn at the same time from the aorta and the coronary sinus, we measured hemoglobin and percentage oxygen saturation with a hemoxymeter (Radiometer SM-2) and calculated oxygen content using an oxygen capacity of 1.39 $ml \cdot g^{-1}$ hemoglobin. The arteriovenous difference across the left ventricle ($ml \cdot l^{-1}$) was then multiplied by the blood flow ($ml \cdot g^{-1} \cdot min^{-1}$) measured simultaneously with radioactive microspheres.

We also estimated myocardial oxygen demand indirectly by two methods. In four experiments, two of the major determinants of myocardial oxygen consumption, wall tension and heart rate, were measured; in addition, maximal positive dP/dt was measured as an index of myocardial contractility. If one simplifies the geometry of the left ventricle to a sphere, then wall tension depends on left ventricular diameter and peak systolic pressure (La Place relationship).[14] We therefore measured left ventricular epicardial diameters and systolic pressure, and estimated peak systolic wall tensions from these data.

In all 11 experiments, we used the rate–pressure product as an indirect index of demand, because this index is easily calculable and has been shown to correlate well with myocardial oxygen consumption during anesthesia.[15] One recent study showed only a fair correlation between the rate–pressure product and

oxygen consumption in patients during halothane anesthesia[16]; in that study, however, the range of variation of rate–pressure products was small, so high correlations with myocardial oxygen consumption could not have been expected. We defined the rate–pressure product as heart rate × peak aortic systolic pressure × 10^{-2} (beats·torr·min^{-1}). To compare myocardial oxygen supply–demand ratios during individual anesthetic regimens, myocardial blood flow was divided by the rate–pressure product and multiplied by 10^{-4} to give units of ml·g^{-1}·torr·beat^{-1}.

Measurement of Myocardial Blood Flow by Use of Microspheres

Six vials of microspheres (9 ± 1 μm or 15 ± 1 μm in diameter, mean ± SD; 3-M Company, St. Paul, Minnesota), labeled with ^{125}I, ^{141}Ce, ^{85}Sr, ^{95}Nb, or ^{46}Sc (all 9 μm) or ^{51}Cr (15 μm) were prepared as previously described.[17] For each myocardial blood flow measurement, we injected 1.8×10^6 to 2.2×10^6 microspheres into the left atrium over 30 seconds. Using a Holter pump, we simultaneously withdrew a 2-minute reference blood sample from the aorta at a constant rate of 30–40 ml·min^{-1} to fill four successive collecting vials for 30 seconds each. Before each microsphere injection, we corrected arterial blood-gas values to maintain stable values of Pa_{CO_2}, Pa_{O_2}, and *p*H, if necessary. When the circumflex coronary artery was constricted, we held the desired pressure in the distal coronary artery constant for 15 seconds before injection and for at least the first 60 seconds during injection of the microspheres. We observed little change in heart rate, P_{LV}, P_{AO}, P_{LVED}, or maximal positive dP/dt during the constriction. There was no atrial or ventricular irritability even during severe constriction.

Upon completing the experiment, we arrested the heart with a concentrated solution of potassium chloride and then removed and weighed it, and fixed it in formalin (10 per cent) for a week. The left ventricle was separated from the rest of the heart, freed of fat, epicardial vessels, and valves, and then divided into free wall and septum. Each of these was divided into apical, middle, and basal portions, which were in turn subdivided into anterior and posterior sections (fig. 2). The posterior sections of the middle and basal portions of the left ventricle were further subdivided into three segments, since this was the area to which the left circumflex coronary artery delivered blood. In addition, each left ventricular and septal segment was cut into six layers of about equal thicknesses from endocardial to epicardial surfaces and from left ventricular to right ventricular septal surfaces, respectively.

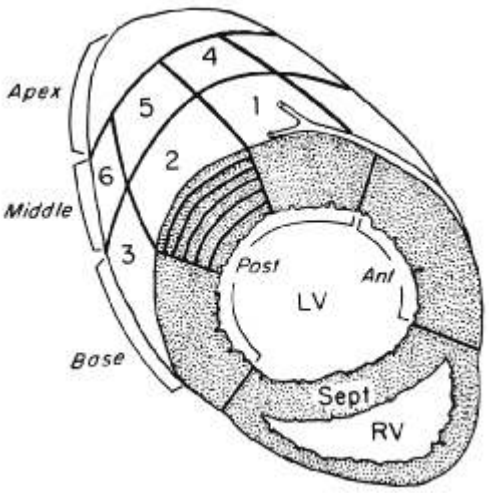

Fig. 2. Sectioning technique of the left ventricular myocardium used for analysis of blood flow by use of microspheres. The major areas of interest were those that received blood flow from the left circumflex coronary artery. These areas were the three posterior basal sections (1–3) and the three posterior middle sections (4–6). The anterior middle and basal sections, which received blood from the unconstricted left anterior descending artery, were compared with the six segments of the posterior middle and basal sections.

The blood samples obtained during microsphere injection and the myocardial tissue samples were counted in a well scintillation counter with a sodium iodide (T1) crystal (Searle Analytic, Inc.) connected to a 512-channel pulse-height analyzer. The total activity of each nuclide was calculated by the stripping method of Heymann *et al.*[17] The total regional blood flows in the heart (ml·min^{-1}) were calculated as the reference blood sample flow (ml·min^{-1}) multiplied by the quotient of counts per minute in the heart or region divided by the counts per minute in the reference sample. Cardiac output (ml·min^{-1}) was calculated as the reference sample flow (ml·min^{-1}) multiplied by the quotient of total counts per minute injected into the left atrium divided by counts per minute in the reference sample. Transmural subendocardial/subepicardial flow ratios were calculated by comparing flow (ml·min·g^{-1}) from the sixth of the left ventricle closest to the endocardium with flow to the sixth of the left ventricle closest to the epicardium. The number of microspheres in each tissue sample was always greater than 400.[17]

Collateral Blood Flow

To assess the possibility that the left anterior descending coronary artery was contributing collateral blood flow during left circumflex coronary arterial constrictions, we measured collateral blood flow by two methods. In three of the original 11 dogs, the

TABLE 1. Stability of Determinants of Myocardial Oxygen Demand with Graded Constrictions of the Left Circumflex Coronary Artery during Autoregulation in 11 Dogs

	Mean Circumflex Arterial Pressure (torr)	Heart Rate (beats·min^{-1})	Mean Aortic Pressure (torr)	Rate–Pressure Product (torr·beats·min^{-1}·10^{-2})	P_{LVED} (torr)	Maximal Positive dP/dt (torr·sec^{-1})
Nitrous oxide						
Control	128 ± 3	171 ± 4	138 ± 5	245 ± 8	5 ± 1	1879 ± 110
Medium constriction	78 ± 2	173 ± 4	138 ± 6	250 ± 8	5 ± 2	1856 ± 114
Severe constriction	34 ± 2	177* ± 4	130*† ± 6	238 ± 8	6 ± 2	1809 ± 117
Halothane						
Control	83 ± 4	146 ± 4	91 ± 4	144 ± 9	5 ± 2	1079 ± 82
Medium constriction	56 ± 3	144 ± 4	89 ± 4	138* ± 8	4 ± 2	1041 ± 77
Severe constriction	28 ± 2	144 ± 5	84*† ± 3	133* ± 9	5 ± 2	1046 ± 78

Hemodynamic data were obtained only at the time of microsphere injections during autoregulation.

Values in all tables are expressed as means ± SEM. Data were analyzed by analysis of variance.

* Significantly different from control, $P < 0.01$.

† Significantly different from medium occlusion, $P < 0.01$.

entire surgical preparation was completed with the addition of an electromagnetic flow transducer and a hydraulic occluder placed at the origin of the left anterior descending coronary artery. At various grades of left circumflex coronary arterial constriction during autoregulation and during maximal vasodilatation for both anesthetic regimens, we transiently totally occluded the anterior descending artery and looked for a decrease in the distal left circumflex coronary arterial pressure. During all grades of circumflex coronary arterial constrictions, we also looked for any increase in left anterior descending arterial blood flow.

For the second method, we prepared three additional dogs in a manner similar to that used for the original 11 dogs. Nitrous oxide was used for anesthesia, and 30 minutes after completion of the preparation, carbochromen (8 mg·kg^{-1}) was given intravenously. Six different pressures in the left circumflex coronary artery were obtained in random order with the occluder. Radioactive microspheres were given at each pressure. Total left circumflex coronary arterial blood flow obtained with the electromagnetic flow transducer was then plotted against circumflex coronary arterial blood flow obtained with the microspheres, and the results were analyzed by linear regression analysis. We expected that any nutrient collateral flow not being measured by the flow transducer would cause deviation of the data points toward the microsphere axis at low flows.

Statistical Analysis

When comparing the effects of the anesthetics during autoregulation on a specific variable such as heart rate, aortic pressure, or myocardial blood flow, we used two-factor analysis of variance. We expressed all values as mean ± standard error of the mean (SEM). Pressure–flow relations during maximal vasodilatation were analyzed with linear regressions by the least-squares method. Ninety-five per cent confidence limits for the slope were obtained and correlation coefficients for each relation were determined. Regressions were tested for linearity by analysis of variance. Slopes and x axis (pressure) intercepts of the maximal vasodilatation line during each anesthetic regimen were compared by analysis of covariance. The point of intersection of the autoregulation and maximal vasodilatation pressure–flow lines for the two anesthetic regimens were compared by use of Student's *t* test for paired data.

Results

Neither the order of administering the anesthetics nor the order of studying autoregulation and maximal vasodilatation appeared to affect the results. Therefore the data from all 11 dogs were pooled.

To permit assessment of steady-state pressure–flow relations, the major determinants of myocardial oxygen demand had to remain stable at each level of coronary arterial perfusion pressure during autoregulation and maximal vasodilatation for both anesthetic regimens. When we compared the values for each determinant at three different circumflex coronary arterial perfusion pressures, we found that the determinants of myocardial oxygen demand did not vary much. The only changes occurred at low pressures: during autoregulation, heart rate increased slightly

TABLE 2. Stability of Determinants of Myocardial Oxygen Demand with Graded Constrictions of the Left Circumflex Coronary Artery during Maximal Vasodilatation in 11 Dogs

	Mean Circumflex Arterial Pressure (torr)	Heart Rate (beats·min^{-1})	Mean Aortic Pressure (torr)	Rate–Pressure Product (torr·beats·min^{-1}·10^{-2})	P_{LVED} (torr)	Maximal Positive dP/dt (torr·sec^{-1})
Nitrous oxide						
Control	97 ± 3	170 ± 6	119 ± 5	216 ± 9	3 ± 0.6	1987 ± 120
Medium constriction	60 ± 2	171 ± 7	119 ± 5	222 ± 12	3 ± 0.7	2063 ± 148
Severe constriction	36 ± 3	177* ± 7	120 ± 5	225 ± 12	4 ± 0.8	1986 ± 113
Halothane						
Control	63 ± 5	142 ± 4	83 ± 4	132 ± 10	3 ± 0.7	1130 ± 81
Medium constriction	48 ± 4	143 ± 4	83 ± 4	132 ± 10	3 ± 0.9	1130 ± 94
Severe constriction	27 ± 2	144 ± 4	82 ± 4	133 ± 9	3 ± 0.5	1099 ± 76

Hemodynamic data were obtained only at single high, medium, and low circumflex-artery pressures during maximal vasodilatation. Data were analyzed by analysis of variance.

* Significantly different from control, $P < 0.01$.

during nitrous oxide anesthesia and mean aortic pressure and the rate–pressure product decreased slightly during both anesthetic regimens (table 1); during maximal vasodilatation, heart rate increased slightly during nitrous oxide anesthesia (table 2).

To permit comparison of pressure–flow relations during autoregulation and maximal vasodilatation, the major determinants of myocardial oxygen demand also had to be similar. The determinants would be similar if carbochromen selectively vasodilated coronary arteries and did not influence systemic determinants of myocardial oxygen demand.[12] For both nitrous oxide and halothane anesthesia, we found that values for heart rate, mean aortic pressure, the rate–pressure product, and P_{LVED} during autoregulation and during maximal vasodilatation were similar (table 3). The only difference was that maximal positive dP/dt was a little higher during maximal vasodilatation than during autoregulation for nitrous oxide anesthesia.

EFFECTS OF NITROUS OXIDE ANESTHESIA AND HALOTHANE ANESTHESIA BEFORE CIRCUMFLEX CORONARY ARTERIAL CONSTRICTIONS (CONTROL STATE)

Systemic Hemodynamics (Table 3). Heart rate, mean aortic pressure, mean left ventricular systolic pressure, the rate–pressure product, maximal positive dP/dt, and cardiac output were significantly lower during halothane anesthesia than during nitrous oxide anesthesia. The P_{LVED} was not significantly different.

TABLE 3. Hemodynamic Effects of Nitrous Oxide Anesthesia and Halothane Anesthesia during Autoregulation and Maximal Coronary Vasodilatation in 11 Dogs

	Heart Rate (beats·min^{-1})	Mean Aortic Pressure (torr)	Mean LV Systolic Pressure (torr)	P_{LVED} (torr)	Rate–Pressure Product (torr·beats·min^{-1}·10^{-2})	Maximal positive dP/dt (torr·sec^{-1})	Cardiac Output (L·min^{-1})
Nitrous oxide							
Autoregulation	173 ± 4	128 ± 6	104 ± 3	2.7 ± 0.5	237 ± 9	1693 ± 120	3.1 ± 0.6
Maximal vasodilatation	175 ± 6	118 ± 5	101 ± 4	3.0 ± 0.8	215 ± 12	1934† ± 105	—
Halothane							
Autoregulation	148* ± 4	87* ± 4	75* ± 5	2.0 ± 0.4	134* ± 7	957* ± 72	2.1* ± 0.7
Maximal vasodilatation	143‡ ± 5	84‡ ± 4	75‡ ± 5	2.3 ± 0.7	124‡ ± 7	1095‡ ± 90	

All hemodynamic data, except cardiac output, were obtained during each recorded pressure–flow relation at every grade of circumflex coronary arterial constriction. Data were analyzed by analysis of variance.

* Significantly different from autoregulation value during nitrous oxide anesthesia, $P < 0.001$.

† Significantly different from autoregulation value during nitrous oxide anesthesia, $P < 0.025$.

‡ Significantly different from maximal vasodilatation value during nitrous oxide anesthesia, $P < 0.001$.

Myocardial Blood Flow (Table 4). Data obtained by the radioactive microsphere method at control pressures during autoregulation showed that total myocardial blood flow and left ventricular blood flow were less by about 40 per cent during halothane anesthesia. However, adjusting left ventricular blood flow (an index of supply) for the rate–pressure product (an index of demand) showed that myocardial oxygen supply–demand ratios during the two anesthetic states were similar. Furthermore, the control transmural subendocardial/subepicardial flow ratios for the left ventricle were similar during the two anesthetic states.

Myocardial Oxygen Demand (Table 5). In the four dogs in which oxygen consumption was measured, arteriovenous oxygen content differences were similar with the two anesthetics, but myocardial oxygen consumption was significantly less during halothane anesthesia, a finding that is consistent with the reduction in left ventricular blood flow. In addition, with each anesthetic regimen, epicardial end-diastolic and peak systolic diameters of the left ventricle in these four dogs during autoregulation and during maximal vasodilatation were not significantly different. Since left ventricular diameters were not different but left ventricular systolic pressure was less during halothane anesthesia (table 3), systolic wall tension was less. Thus, the major determinants of myocardial oxygen consumption—wall tension, heart rate, and contractile state as measured by maximal positive dP/dt (table 3)—all were less during halothane anesthesia. In all 11 dogs, the rate–pressure product was significantly less with halothane.

Pressure–Flow Relations for the Left Circumflex Coronary Artery

Autoregulation. Blood flow in the left circumflex coronary artery remained relatively constant over a wide range of perfusion pressures during both anesthetic states (fig. 3). However, eventually a perfusion pressure was reached at which the ability of the vessel to regulate flow became exhausted; at this point, the breaking point (fig. 3, N_3, H_3), flow began to decrease quite rapidly. Perfect autoregulation, *i.e.*, steady-state flow that does not change at all with changes in perfusion pressure, did not occur: the autoregulation lines (fig. 3, N_2, H_2) had a gentle slope as pressure decreased from the control value to the breaking point. Linear regression analysis of the pressure–flow relations above the breaking points showed consistently small but significant positive slopes during both anesthetic regimens (halothane: 0.10 ± 0.06 SEM; nitrous oxide: 0.13 ± 0.03 SEM; n = 11).

Over the range of coronary arterial pressures at which autoregulation took place, myocardial blood flow was consistently less during halothane than during nitrous oxide anesthesia (fig. 3). However, when the autoregulated blood flows with the two anesthetics were divided by an index of oxygen demand (the rate–pressure product), as done for left ventricular blood flow measured by use of microspheres at baseline pressures, the autoregulated portions of the pressure–flow curves were superimposed.

Maximal Vasodilatation. During maximal vasodilatation, pressure–flow relations for each anesthetic were consistently linear ($P < 0.01$), and always had correlation coefficients greater than 0.93 (nitrous oxide: mean 0.98 ± 0.01 SEM; halothane: mean 0.97 ± 0.01 SEM) and narrow 95 per cent confidence limits. The slope (flow–pressure) of this linear regression line represents vascular conductance (resistance^{-1}) and the pressure (x axis) intercept predicts the pressure at which zero flow occurs. The slopes of the maximal vasodilatation lines for the two anesthetics were similar (fig. 4) according to analysis of covariance (halothane: 5.0 ± 0.03 SEM; nitrous oxide: 5.2 ± 0.04 SEM), but the zero-pressure axis intercepts were significantly lower for halothane (18.5 ± 1.7 SEM) than for nitrous oxide (27.5 ± 1.7 SEM), and the maximal vasodilatation line for halothane was always to the left of the nitrous oxide line. In this study the maximal

TABLE 4. Myocardial Blood Flows in the Control State Determined by the Microsphere Method of Nitrous Oxide Anesthesia and Halothane Anesthesia during Autoregulation in Eight Dogs (Circumflex Coronary Artery Not Constricted)

	Total Myocardial Blood Flow ($ml \cdot g^{-1} \cdot min^{-1}$)	Left Ventricular Blood Flow ($ml \cdot g^{-1} \cdot min^{-1}$)	Rate–Pressure Product (RPP) ($torr \cdot beats \cdot min^{-1} \cdot 10^{-2}$)	Left Ventricular Flow/ RPP·10^{-4} ($ml \cdot g^{-1} \cdot torr \cdot beats^{-1}$)	LV Endocardial/ Epicardial Flow Ratio
Nitrous oxide	0.94 ± 0.10	1.07 ± 0.10	245 ± 8	43 ± 5	1.03 ± 0.10
Halothane	0.62* ± 0.10	0.63* ± 0.11	144* ± 9	45 ± 5	1.00 ± 0.10

Data were analyzed by analysis of variance.

* Significantly different from value obtained with nitrous oxide, $P < 0.005$.

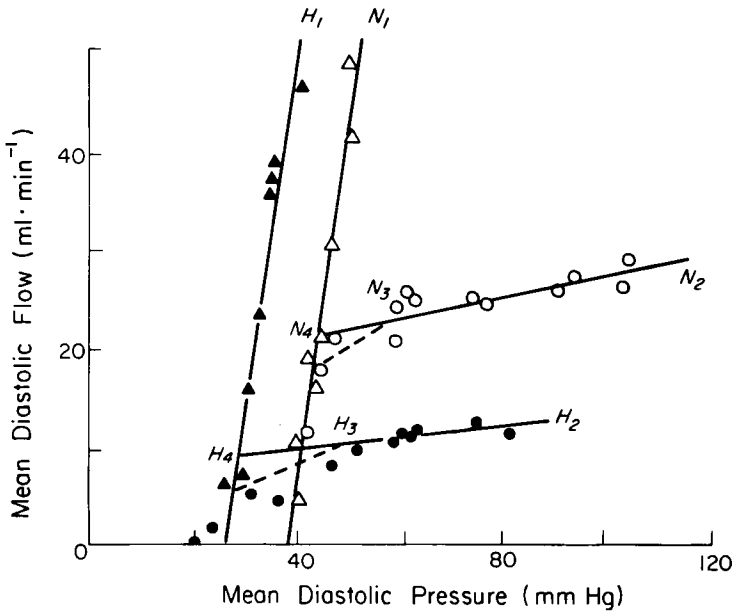

FIG. 3. Pressure–flow relations in one dog anesthetized first with halothane (H, ▲, ●) and then with nitrous oxide (N, △, ○). H_1, N_1, pressure–flow relations during maximal vasodilatation; H_2, N_2, pressure–flow relations during autoregulation; H_3, N_3, breaking point; H_4, N_4, point of intersection.

vasodilatation line remained linear even at low coronary arterial perfusion pressures.

The diastolic pressure at which the lines obtained by linear regression during maximal vasodilatation (fig. 3, H_1, N_1) and autoregulation (fig. 3, H_2, N_2) met was defined as the "point of intersection" (fig. 3, H_4, N_4). The point of intersection occurred at a lower diastolic pressure during halothane anesthesia (27.7 ± 2.3 SEM) than during nitrous oxide anesthesia (42.0 ± 3.3 SEM). In all experiments, the breaking point (fig. 3, H_3, N_3) occurred at a slightly higher pressure than the point of intersection, probably because the loss of autoregulatory tone does not occur simultaneously in all vessels across the wall of the left ventricle. Rouleau *et al.*[18] have recently shown that the subepicardium maintains its ability to vasodilate at a myocardial supply–demand ratio which has already caused the subendocardium to be maximally vasodilated. Data points obtained during autoregulation below the point of intersection in each anesthetic state were nearly superimposed on the corresponding maximal vasodilatation line.

Blood flow data obtained at three circumflex coronary arterial pressures by the radioactive microsphere method showed that for both anesthetics, blood flows in the combined middle and basal portions of the posterior left ventricle, which are supplied by the left circumflex coronary artery (fig. 2), and the subendocardial/subepicardial flow ratios remained stable above the breaking point but fell sharply below the breaking point (table 6). Results were similar for each of the six areas of interest separately. Consistent with the data obtained by use of the electromagnetic flow transducer, regional blood flows obtained by use of radioactive microspheres were less during halothane anesthesia than during nitrous oxide anesthesia, and the breaking point occurred at a lower diastolic pressure. Simultaneous measurements of blood flow

TABLE 5. Nitrous Oxide and Halothane Anesthetic Effects on Left Ventricular Diameter and Myocardial Oxygen Consumption in the Control State in Four Dogs (Circumflex Coronary Artery Not Constricted)

	Epicardial Left Ventricular Diameter (mm)				Coronary a-v O_2 Content Difference (ml $O_2 \cdot 100\ g^{-1}$)	Myocardial Oxygen Consumption (ml $O_2 \cdot g^{-1} \cdot min^{-1}$)
	Autoregulation		Maximal Vasodilatation			
	End Diastolic	Peak Systolic	End Diastolic	Peak Systolic		
Nitrous oxide	53.3 ± 2.0	49.9 ± 1.8	53.6 ± 2.1	50.5 ± 1.7	10.9 ± 0.03	0.11 ± 0.01
Halothane	53.7 ± 1.7	51.0 ± 2.0	53.7 ± 2.0	50.5 ± 1.9	9.5 ± 2.0	0.05* ± 0.01

Data were analyzed by analysis of variance.

* Significantly different from value obtained with nitrous oxide, $P < 0.01$.

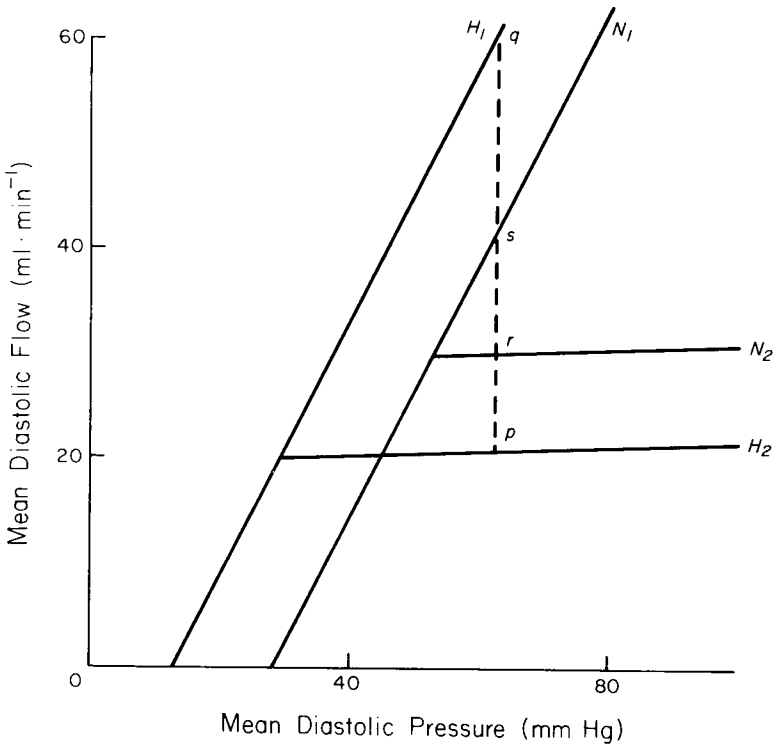

FIG. 4. Composite pressure–flow relations in 11 dogs anesthetized with halothane or nitrous oxide. H_1, N_1, pressure–flow relations during maximal vasodilatation; H_2, N_2, pressure–flow relations during autoregulation. The slopes of the maximal vasodilatation lines are similar (H_1: 5.0 ± 0.03 SEM; N_1: 5.2 ± 0.04 SEM) but the pressure–axis intercepts are significantly different (H_1: 18.5 ± 1.7 SEM; N_1: 27.5 ± 1.7 SEM). At a perfusion pressure of 60 torr, the coronary vascular reserve during halothane anesthesia is represented by q-p; the coronary vascular reserve during nitrous oxide anesthesia at the same pressure is represented by s-r.

in the anterior left ventricular wall supplied by the unconstricted left anterior descending artery (middle and basal sections combined) showed no change in the blood flow or subendocardial/subepicardial ratio at any grade of constriction involving the circumflex coronary artery.

Collateral Blood Flow

In each of the three plots of blood flow as measured with radioactive microspheres against electromagnetic transducer measured flow, the relationship was linear, the correlation coefficient was high (0.98 ± 0.05 SEM), and the intercept was not significantly different from the origin. The line did not deviate toward the microsphere axis at low flows.

Distal left circumflex coronary arterial pressure did not change during any arterial constriction or during any transient total occlusion of the left anterior descending artery at any circumflex coronary arterial pressure. Left anterior descending arterial blood flow did not increase during left circumflex coronary arterial constriction lasting as long as 2 minutes.

Discussion

Anesthetic Regimens

In order to create two different, readily reversible circulatory states without the use of specific cardiovascular stimulants or blocking agents, we chose two inhalational anesthetic regimens: 75–80 per cent nitrous oxide in oxygen and 0.8 per cent halothane in oxygen. Seventy-five per cent nitrous oxide represents a subanesthetic concentration in the dog; however, the combination of a large dose of thiopental (25 $mg \cdot kg^{-1}$) during the surgical procedure, nitrous oxide (75–80 per cent), muscle paralysis (pancuronium bromide, 0.1 $mg \cdot kg^{-1}$), and artificial ventilation resulted in a hemodynamic state characterized by a normal or elevated aortic pressure and heart rate and unchanged myocardial contractility. This anesthetic technique provided good operating conditions without movement in most dogs, although rarely, additional doses of thiopental (3–4 $mg \cdot kg^{-1}$) or pancuronium bromide (0.05 $mg \cdot kg^{-1}$) were given during the surgical preparation. When the nitrous oxide study followed the halothane study small concentrations (0.1–0.2 per cent) of halothane were usually still present. Since these results were similar to those obtained when nitrous oxide was given first, the low concentrations of halothane caused no significant change in the results. In the dog, an end-expiratory concentration of halothane of 0.8 per cent produces light anesthesia, which resulted in a hemodynamic state characterized by reductions in aortic pressure, heart rate, and myocardial contractility. Again, we rarely needed additional doses of muscle relaxant, especially once the active phases of the surgical preparation were complete.

Critique of Experiments

Circumflex Coronary Arterial Pressure and Pulse Pressure. Coronary arterial pressure was frequently 5–25 torr less than aortic pressure after injection of carbochromen. This difference was probably secondary to the increase in flow through the fixed diameter (resistance) of the flow transducer. At the end of the experiment, this difference in pressures could be diminished by removing the flow transducer, but a residual small difference (less than 5 torr) between coronary arterial pressure and aortic pressure was often present with both nitrous oxide (fig. 5*a*) and halothane anesthesia.

The pulse pressure of the circumflex coronary artery widened during partial hydraulic constriction, probably because the occluder at the origin of the circumflex artery produces a resistance that affects coronary arterial diastolic pressure more than systolic pressure (fig. 5*b*). In systole, with its low flows, there is little pressure drop across the resistance, so that distal coronary arterial systolic pressure decreases minimally. However, in diastole, with its high flows, there is a large pressure drop across the resistance, which causes diastolic pressure to decrease faster than mean pressure. The resultant widening of the pulse pressure continues as the resistance of the occluder increases until diastolic flow begins to decrease, at which time the pulse pressure begins to narrow. A widened pulse pressure distal to coronary arterial stenosis is consistent with the findings of Gould and Lipscomb.[19]

Neither the reduction in circumflex coronary arterial pressure by carbochromen nor the widening of the pulse pressure during partial hydraulic constriction should have affected the pressure–flow relations, which are based on observed diastolic pressures and blood flows.

Collateral Blood Flow. If collateral blood had flowed into the circumflex coronary arterial distribution distal to the occluder, either during any single circumflex coronary arterial constriction or during the experiment after several constrictions, pressure–flow relations obtained with the flow transducer would have been inaccurate. Since most collateral blood flow to the circumflex coronary artery develops from flow in the left anterior descending artery,[20] investigators have measured changes in circumflex coronary arterial pressure over time as indices of functional collateral flow.[20–23] In our study, once distal circumflex coronary arterial pressure had been lowered by partial constriction, it did not increase over the next 5 minutes or decrease during a transient total occlusion of the anterior descending artery, nor did flow in the anterior descending artery increase at any time. In addition, the plots of blood flows obtained by the flow transducer and flows obtained by use of microspheres during maximal vasodilatation in each of three dogs were linear even for low flows. Similar results have been found by others.[20–23] It is thus unlikely that collateral blood flow from the anterior descending artery influenced the pressure–flow relations obtained in the distribution of the circumflex coronary artery either during a constriction or over the four-hour experiment.

Regional Myocardial Function. To compare the steady-state relationships of altered coronary arterial perfusion pressures and resultant blood flows during different anesthetic regimens, regional myocardial

Table 6. Microsphere Blood Flow Data at Three Grades of Constriction of the Left Circumflex Coronary Artery during Autoregulation in Eight Dogs

	Mean Circumflex Arterial Pressure (torr)	Posterior Left Ventricular Flow ($ml \cdot g^{-1} \cdot min^{-1}$)	Posterior LV Subendocardial/ Subepicardial Flow Ratio	Anterior Left Ventricular Flow ($ml \cdot g^{-1} \cdot min^{-1}$)	Anterior LV Subendocardial/ Subepicardial Flow Ratio
Nitrous oxide					
Control	126 ± 3	1.2 ± 0.2	1.2 ± 0.1	1.1 ± 0.2	1.4 ± 0.2
Medium constriction	87 ± 3	1.4 ± 0.1	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.1
Severe constriction	40 ± 2	0.6* ± 0.1	0.5* ± 0.1	0.9 ± 0.1	1.3 ± 0.1
Halothane					
Control	85 ± 5	0.8 ± 0.2	0.9 ± 0.1	0.7 ± 0.1	1.3 ± 0.1
Medium constriction	61 ± 3	0.7 ± 0.1	1.1 ± 0.1	0.6 ± 0.1	1.2 ± 0.1
Severe constriction	28 ± 2	0.4* ± 0.1	0.5* ± 0.1	0.6 ± 0.1	1.0 ± 0.2

Data were analyzed by analysis of variance.

* Significantly different from control and from value obtained for medium grade of constriction, $P < 0.001$.

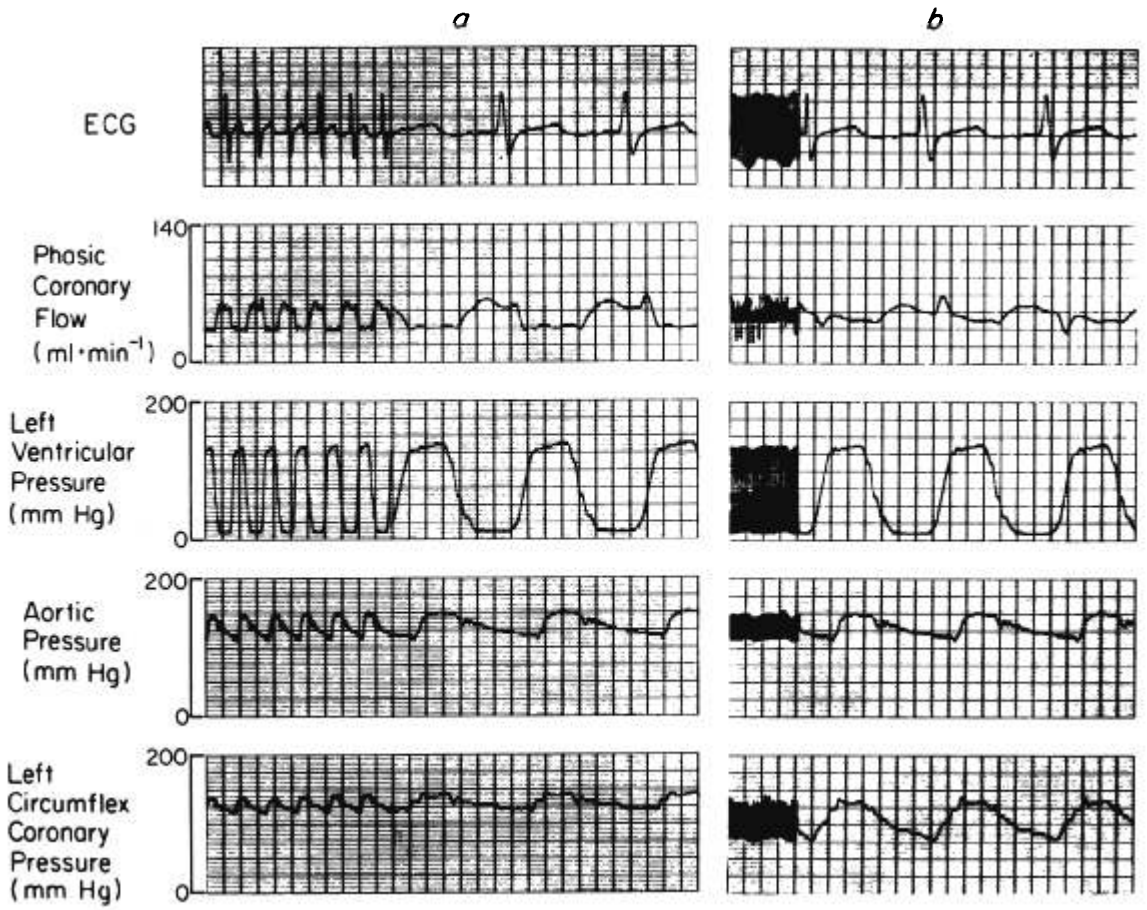

FIG. 5. Typical strip chart recording of systemic pressures and left circumflex coronary arterial pressure–flow relations with autoregulation during nitrous oxide anesthesia. *a*, control (no constriction of the circumflex coronary artery). Notice the small drop in pressure from aorta to circumflex coronary artery. *b*, lower circumflex coronary arterial pressure due to medium-grade constriction of the circumflex coronary artery. Notice the widened pulse pressure in the circumflex coronary artery during partial constriction.

dysfunction distal to the constriction must be minimal at all perfusion pressures. Regional myocardial dysfunction during partial constriction has been demonstrated only when regional coronary arterial pressures are less than 50 torr or regional coronary arterial blood flows are less than 30 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.[24–26] Some pressures and flows in our study that were below these levels. We did not measure regional function; however, there were only minor changes in global ventricular function at these times. During autoregulation, severe constrictions (table 1) caused only a 3.1 per cent increase in heart rate, a 6.0 per cent decrease in mean aortic pressure, and a 3.2 per cent decrease in the rate–pressure product at the time of microsphere injection. The P_{LVED} and maximal positive dP/dt did not change. During maximal vasodilatation only heart rate increased (by 3.9 per cent). Thus, many of the global factors that are known to affect pressure–flow relationships were relatively unchanged during even severe constrictions. Furthermore, since for each dog the blood flows at the low pressures fell on the same pressure–flow line that had been defined at higher flow rates during maximal vasodilatation, it did not appear that any regional dysfunction present substantially altered the pressure–flow relationships. Since all constrictions lasted less than 30 seconds when the flow transducer was used and less than 90 seconds when microspheres were injected, regional dysfunction, if present at all, was probably reversible and not progressive throughout the experiment.

Pressure–Flow Relations during Autoregulation. Autoregulation keeps blood flow relatively constant over a wide range of perfusion pressures by changing coronary vascular resistance in parallel with changes in pressure.[27] Both nitrous oxide and halothane preserved the autoregulatory mechanism. However, perfect autoregulation of blood flow, as previously reported,[18,28] did not occur in this study; the slope of myocardial blood flow was slightly positive in the autoregulatory range of pressures during anesthesia with both anesthetics, a phenomenon also described by others.[28] One possible explanation is that flow was in fact constant, but that at low perfusion pressures

some of the flow came from collateral sources and was not recorded by the flowmeter; this possibility has been excluded. Another possible explanation for this slope is that as perfusion pressures fell, the myocardium regulated oxygen delivery by increasing oxygen extraction slightly and thus decreasing flow.[29] Weber *et al.*[29] recently showed that myocardial oxygen extraction can increase from 65–75 per cent to 90 per cent when coronary arterial stenosis is present; but whether this increase in extraction is secondary to a reduction in flow or whether the reduction in flow is secondary to the increased oxygen extraction in not clear. Another possible explanation is that some vessels closed due to derecruitment of tissue as perfusion pressure decreased.[30] This would signify a constant blood flow per unit of tissue, but with fewer units perfused at lower pressures.

Myocardial Oxygen Supply–Demand Balance and Coronary Vascular Reserve

Systemic Hemodynamics. The general systemic changes found with halothane (0.8 per cent end-tidal concentration) in this study are consistent with those described in previous reports, in that heart rate, mean left ventricular and aortic pressures, the rate–pressure product, positive maximal dP/dt, cardiac output, and total myocardial blood flow were less during halothane anesthesia than during nitrous oxide anesthesia.[7,31,32] In conscious animals, halothane anesthesia at end-tidal concentration of 0.79 to 1.0 per cent causes similar hemodynamic changes, except for those in heart rate.[33–35] Merin *et al.*[33] and Vatner *et al.*[34] both reported slight increases in heart rate in dogs at 0.79 per cent and 1.0 per cent halothane concentrations, respectively, but Amory *et al.*[35] found a slight decrease in heart rate at a 1 per cent halothane concentration in restrained monkeys. Most of these findings have been attributed to primary myocardial depression during halothane anesthesia.[7,31–34,36–38]

Relationship of Myocardial Oxygen Supply and Demand. Myocardial oxygen demand was less during halothane anesthesia than during nitrous oxide anesthesia when measured directly or estimated indirectly. This reduced oxygen demand with halothane is consistent with the findings of others,[7,31,33,36–38] but controversy exists about whether this reduction is beneficial. Smith *et al.*[7] found a small increase in myocardial oxygen extraction and concluded that the reduced oxygen demand with halothane was not beneficial because halothane decreased myocardial oxygen supply more than it decreased myocardial oxygen demand. In contrast, Weaver *et al.*[31] and Wolff *et al.*[36] found decreases in myocardial oxygen extraction, and Wolff *et al.*[36] concluded that during halothane anesthesia sufficient oxygen was delivered through an autoregulatory mechanism to meet myocardial demand. Our experiments confirm this conclusion. We found that values for myocardial oxygen extraction were similar with the two anesthetic regimens, and when we adjusted myocardial oxygen supply (left ventricular blood flow) for an index of oxygen demand (the rate–pressure product), the supply–demand ratios for the two anesthetics became similar.

If autoregulation of coronary arterial blood flow is intact with halothane and nitrous oxide regimens, and myocardial supply matches oxygen demand, then the alleged benefits of halothane anesthesia during ischemia[5,6] are not explained. It is not until the effects of maximal vasodilatation are examined that a reason for the possible superiority of halothane becomes apparent. This analysis involves considering not only the slope of the pressure–flow relationship during maximal vasodilatation (*i.e.*, resistance), but also the intercepts that these lines make with the pressure axis and the methods of calculating coronary vascular resistance.

When the pressure–flow line obtained with maximal vasodilatation during for anesthetic regimen was extrapolated to the pressure axis, the zero-flow pressure intercept was consistently well above atrial or coronary sinus pressure (18.5 or 27.5 torr). Others have also found intercept pressures of 20 or 30 torr.[39,40] Rouleau *et al.*,[18] on the basis of an investigation using a Gregg cannula in the left main coronary artery, concluded that the zero-flow pressure intercept on the pressure axis occurred at about 20 torr in subendocardial muscle and near zero in subepicardial muscle.

The pressure at which zero flow occurs is probably explained by a vascular waterfall.[41,42] Based on the waterfall concept, the effective downstream pressure (P_2) is not outflow pressure (atrial or coronary sinus pressure) but rather the pressure surrounding the collapsible vessels in the ventricular wall (P_T). Thus, in the left ventricle, the waterfall pressure during maximal vasodilatation probably reflects some average intramyocardial tissue pressure during diastole.The latter pressure presumably corresponds to the zero-flow pressure intercept. In our experiments, intramyocardial tissue pressure was significantly lower during halothane anesthesia (18.5 torr) than during nitrous oxide anesthesia (27.5 torr). The reason for the difference between these intercept pressures during the two anesthetic regimens is unknown.

If the diastolic waterfall, or tissue pressure, is as high as suggested in these and other studies, then there are major implications for calculating and interpreting calculations of coronary vascular resistance. Classically, calculations of coronary vascular resistance have been based on Ohm's law: resistance = pressure

drop ($P_1 - P_2$) divided by flow. When applying this to the coronary vascular bed, most investigators take P_1 to be mean or diastolic aortic or coronary arterial pressure, P_2 to be mean atrial or coronary sinus pressure, and flow to be coronary mean or diastolic flow. These investigators have consistently reported a minimal change or a greater coronary vascular resistance during halothane anesthesia than during anesthesia induced by other agents (or in unanesthetized animals).[7,31,33–36] Smith *et al.*[7] concluded that the greater coronary vascular resistance accounted for the decreased oxygen availability that they found during halothane anesthesia. However, if the diastolic pressure drop across the left ventricular vascular bed is from coronary arterial pressure (P_1) to waterfall pressure (P_T), then calculated vascular resistance does not change even when flow and perfusion pressure are low. For this reason, a one-point determination of resistance can be very misleading. Consider, for example, that in figure 4, the coronary sinus pressure (not shown) was 5 torr. For the nitrous oxide line (N_1), flows of 60 and 40 ml·min^{-1} correspond to mean diastolic pressures of 76 and 59 torr, respectively. Resistances calculated conventionally with coronary sinus pressure as P_2 are $(76 - 5)/60 = 1.18$ torr·ml^{-1} min at the higher perfusion pressure and $(50 - 5)/40 = 1.35$ torr·ml^{-1} min at the lower perfusion pressure, leading to the conclusion that resistance is higher at the lower perfusion pressure. In contrast, calculating resistances with the waterfall pressure of 25 torr as P_T gives a resistance of 0.85 torr·ml^{-1} min at both pressures.

In the experiments reported here, we have confirmed that during maximal vasodilatation the pressure–flow relationship is linear,[39,40] and have added the observation that the slopes of this line, which is vascular conductance (resistance^{-1}), were similar for the halothane and nitrous oxide anesthetic regimens. It is very likely, therefore, that the increases in resistance reported by others are due to neglecting the waterfall pressure and failing to measure resistances at several different pressures. Changes in coronary vascular resistance therefore do not account for the decrease in ischemia during halothane. Changes in diastolic intramyocardial tissue pressure, however, might account for the decrease by increasing effective coronary perfusion pressure and flow at lower coronary arterial pressures.

Coronary Vascular Reserve. At any perfusion pressure, the vertical distance between the autoregulation and maximal vasodilatation lines is a measure of reserve for further vasodilatation. Myocardial blood flow was less during autoregulation and the pressure-axis intercept was lower during maximal vasodilatation with halothane than with nitrous oxide. As a result, the distance between the autoregulation and the maximal vasodilatation lines at any perfusion pressure was always greater for halothane (fig. 4, p–q) than for nitrous oxide (fig. 4, r–s) and, therefore, more coronary vascular reserve was present during halothane anesthesia. For example, at control mean diastolic coronary arterial pressures of 63 and 86.5 torr for the halothane and nitrous oxide regimens, respectively (table 2), the average coronary vascular reserve was 348 per cent more than control flow for halothane and 278 per cent more for nitrous oxide. Thus, despite the lower control perfusion pressure observed during halothane anesthesia, the coronary vascular reserve was actually greater than that during nitrous oxide anesthesia. It is important to note that this advantage was retained during coronary arterial narrowing.

Another way of comparing the two anesthetic regimens is to examine how much pressure can decrease from control levels before autoregulation is lost. For the nitrous oxide regimen, autoregulation was exhausted at a mean diastolic pressure of 42 torr; this is 44.5 torr below control pressure, or a percentage reduction of 56 per cent. For the halothane regimen, autoregulation was lost at a mean diastolic pressure of 27.7 torr; this is 35.3 torr below the control pressure, or a percentage reduction of 51 per cent. Thus, although the absolute pressure reserve was greater for the nitrous oxide regimen, the percentage reductions were similar for the two regimens, and the absolute pressure at which autoregulation was retained was considerably lower for halothane anesthesia.

These considerations indicate that a reduction in myocardial oxygen supply is better tolerated in dogs during light halothane anesthesia than during nitrous oxide anesthesia. The mechanism for this improved tolerance appears to be a lessening of myocardial oxygen demand and a lowering of the diastolic vascular waterfall pressure of the left ventricle, thus increasing the coronary vascular reserve. We do not believe that the effect is specific for halothane, because in studies in progress, pacing the heart at a faster rate while using 0.8 per cent halothane anesthesia decreases the coronary vascular reserve to match that found during the nitrous oxide regimen.

Thus, the effects that we have described do not appear to be specific to the anesthetic regimens used, but rather due to the effects that they induce in the cardiovascular system.

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