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Effect of Halothane on Coronary Collateral Circulation

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The authors studied the effect of halothane in a canine model of coronary collateral circulation secondary to chronic occlusion of a coronary artery. Two sets of experiments were performed. In the first experiments, Ameroid® constrictors were placed around the left anterior descending coronary artery to produce complete occlusion in three weeks. An inflatable occluder was placed around the circumflex coronary artery in order to apply a mild stenosis to the artery supplying the collateral vessels to produce vasodilation distal to the stenosis. Regional myocardial blood flows were measured using radioactive microspheres. Blood flows to normal and collateralized myocardium were decreased significantly during halothane anesthesia, but perfusion of the subendocardium in both regions was maintained even in the presence of mild stenosis of the circumflex coronary artery supplying the collateral vessels, as indicated by unchanged endocardial/epicardial blood flow ratios. In the second experiments, chronic occlusions of both circumflex and right coronary arteries were produced using Ameroid constrictors. In these animals, sedated using xylazine, pacing-induced tachycardia produced a marked but reversible decrease in blood flow to the collateralized subendocardium. During halothane anesthesia at normal heart rate, blood flow to the collateralized subendocardium was well maintained, but tachycardia produced marked decrease in blood flow to the collateralized subendocardium, leading to the demise of four of seven dogs. The authors conclude that in this chronic canine model, in which control measurements were made during sedation using xylazine, coronary collateral blood flow is well maintained during halothane anesthesia at normal heart rate, but tachycardia during halothane anesthesia severely limits blood flow to the collateralized subendocardium. (Key words: Anesthetics, volatile: halothane. Heart: blood flow, myocardial; coronary occlusion.)

THE EFFECTS OF HALOTHANE on myocardial ischemia and infarction have been studied in animals with acute coronary stenosis or occlusions.[1–4] However, in humans, coronary stenosis or occlusion often occurs gradually, which allows time for preexisting collateral vessels to grow and develop.[5] Regions of myocardium in the distribution of narrowed or occluded coronary arteries then may become critically dependent on chronically developed collateral circulation for blood flow.[5] Vasodilators such as lidoflazine and phentolamine produce a "steal phenomenon" in animals with chronic occlusions of a coronary artery by diverting blood flow away from the collateralized myocardium.[6,7] The effect of halothane on collateral circulation developing as a result of chronic occlusion of coronary arteries has not been studied. Litvak *et al.* described a technique of producing chronic coronary artery occlusion in dogs without producing infarction by implanting a constrictor made of Ameroid®, a hygroscopic material, around a coronary artery.[8] Slow swelling of Ameroid® produces gradual stenosis, progressing to occlusion of the artery enclosed by it in 2 to 3 weeks, which allows sufficient time for collateral vessel development so that myocardial infarction does not always occur. This model has been studied extensively by Schaper.[5] We used the radioactive microsphere technique in this model to study the effect of halothane on collateral blood flow in the myocardium.

Materials and Methods

Two different experimental preparations were used. In the first, we occluded the left anterior descending coronary artery chronically and created a reversible stenosis in the circumflex coronary artery in order to produce vasodilation distal to the stenosis in the vessel supplying the collateral bed so that we could search for evidence of "steal phenomenon" during halothane anesthesia. This also simulated multiple lesions often seen in humans. In the second preparation we chronically occluded both circumflex and right coronary arteries and paced the heart at high rates to produce ischemia in the collateralized region. Adult mongrel dogs of either sex weighing 20–25 kg were used for both experiments.

Multiple Lesions Experiments

Under halothane anesthesia, the heart was exposed through a left thoracotomy. The left anterior descending coronary artery was dissected free of connective tissue close to its origin and an Ameroid constrictor of appropriate size encased in a stainless steel ring was placed around it as described by Litvak.[8] The circumflex coronary artery also was dissected free, and an electromagnetic flow probe of appropriate size (Zapeda Instruments) was placed around it. Just distal to the flow probe, an inflatable cuff occluder (Rhodes Medical Instruments) also was placed around the circumflex coronary artery. A polyethylene catheter was inserted into the left atrium. The experimental preparation is shown in figure 1. All

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tubes and wires were brought out through a dorsal stab wound. The chest was closed in layers after evacuation of air in the pleural cavity. The surgical wound, tubes, and wires were protected with a commercial dog jacket, and the dogs were allowed to recover for 3–4 weeks in their kennels. During the first week, penicillin and streptomycin were administered intramuscularly. During the weeks of recovery, the dogs also were brought to the laboratory at regular intervals and trained to lie quietly on their sides on the table.

The experiments were performed 3–4 weeks after surgical preparation. Under thiopental sedation, 100–200 mg intravenously, a 16-gauge catheter was inserted percutaneously into the right femoral artery. The electromagnetic flow probe on the circumflex coronary artery was connected to a flow meter (Zapeda Instruments). Arterial and left atrial pressures, circumflex coronary blood flow, and the electrocardiogram were recorded continuously. After allowing approximately 60 min for recovery from thiopental, control measurements, including arterial *p*H and gas tensions, were made with the animal awake and breathing room air. Repeated determinations of cardiac outputs were made using the dye (indocyanine green) dilution technique until two consecutive determinations were within 10% of each other. Indocyanine green was injected into the left atrial catheter, and arterial blood was sampled from the femoral artery. Regional myocardial blood flow measurements were made using the radioactive microsphere technique as described below.

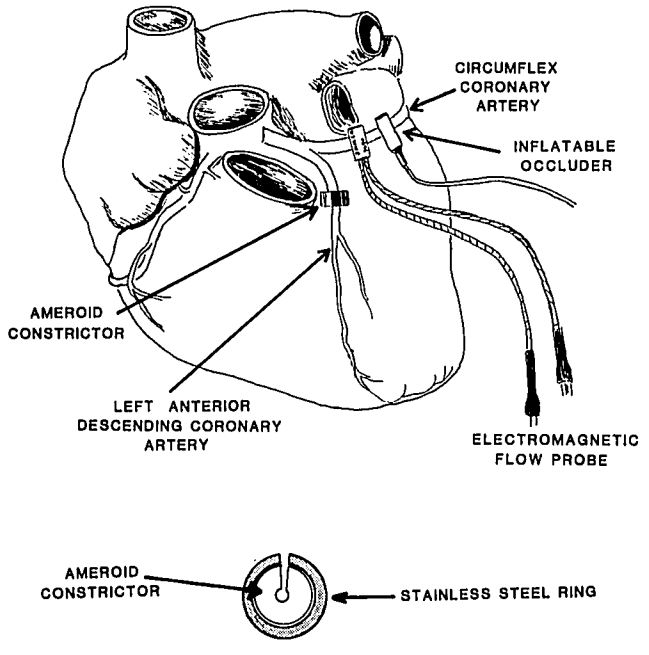

FIG. 1. Surgical preparation for multiple-lesion experiments showing Ameroid constrictor on the left anterior descending coronary artery, electromagnetic flow probe and inflatable occluder on the circumflex coronary artery. A transverse view of an Ameroid constrictor encased in a stainless steel ring also is shown at the bottom.

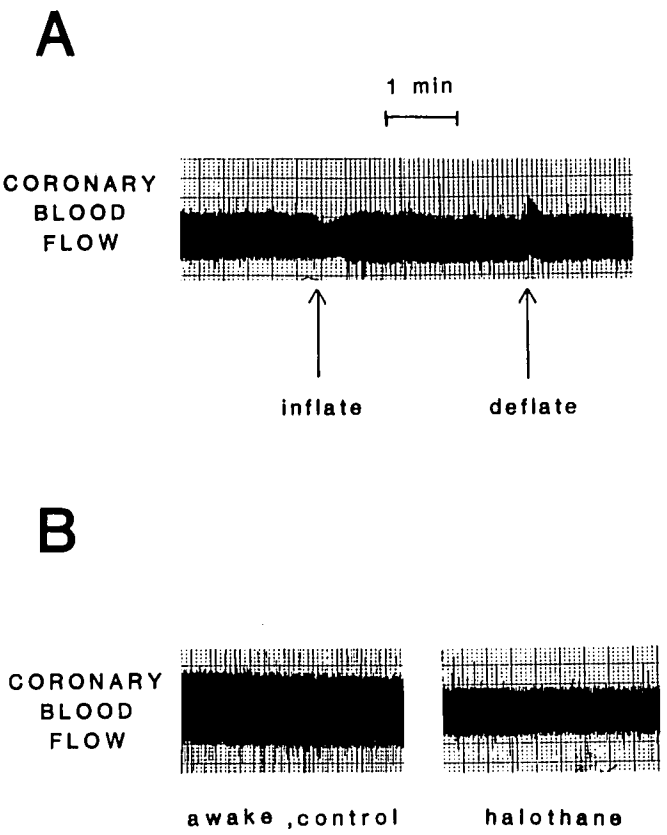

FIG. 2. *A.* Representative recording of flow signals in the circumflex coronary artery in a dog with inflation and deflation of an inflatable occluder to apply and release mild stenosis. Note transient 10–15% decrease in flow signals on inflation and hyperemic response on deflation of inflatable occluder. *B.* Representative recording of flow signals in the circumflex coronary artery in a dog during awake control state and during halothane anesthesia.

After control measurements, a stenosis was applied to the circumflex coronary artery by controlled inflation of the cuff occluder to produce an immediate 10–15% decrease in circumflex coronary blood flow as measured by the electromagnetic flow meter. Vasodilation distal to the stenosis (autoregulation) usually restored blood flow within 1–2 min, as shown in figure 2. Release of stenosis by deflation of the cuff resulted in a hyperemic response, which also subsided within 1–2 min. After testing reproducibility of the stenosis by repeated inflations and deflations of the cuff, stenosis was maintained for 5–10 min, while a second set of hemodynamic and regional myocardial blood flow measurements was made.

Anesthesia then was induced with thiopental 10 mg/kg intravenously and the trachea intubated following intravenous succinylcholine, 1 mg/kg. The animals were ventilated mechanically using a tidal volume of 10 ml/

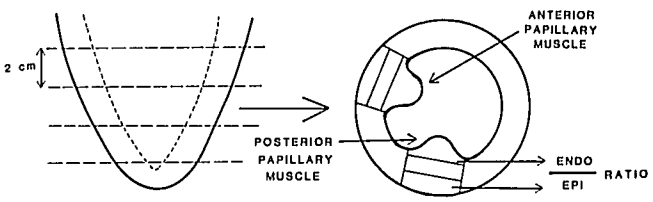

FIG. 3. Schematic representation of serial sections of the left ventricle and transmural samples from anterior and posterior papillary muscle regions.

kg and a rate adjusted to yield Pa_{CO_2} values close to awake control values. Anesthesia was maintained with halothane 1% end tidal (approximately 1.3 MAC) in oxygen measured continuously using a Beckman® infrared analyzer. After approximately 1 h of stable halothane anesthesia, a third set of hemodynamic and regional blood flow measurements was made. Finally, a stenosis of similar severity was applied to produce an immediate but transient 10–15% decrease in circumflex coronary blood flow and a fourth set of hemodynamic and regional blood flow measurements was made.

Regional blood flow measurements were made using 15-μm microspheres labeled with one of the following isotopes: ^{46}scandium, ^{95}niobium, ^{85}strontium, and ^{51}chromium. For each determination, a suspension of approximately 2–3 million of one of the isotope-labeled microspheres was injected into the left atrial catheter. To ensure even dispersion of the microspheres in the suspension, they were placed in an ultrasonic mixer for at least 30 min prior to injection. A reference sample of arterial blood was withdrawn at a constant rate (6.2 ml/min) from the femoral artery for 3 min beginning 10 s before microsphere injection using a Harvard® pump. At the end of the experiment, the animal was killed using potassium chloride injection and the heart was removed. Complete occlusion of the left anterior descending coronary artery was confirmed by inability to pass a 0.5-mm probe either antegrade or retrograde past the Ameroid constrictor. The Ameroid constrictor also was removed and inspected for transmission of light through its channel, visually confirming complete occlusion. The heart was sectioned serially perpendicular to the apex base axis at 2-cm intervals (fig. 3). Animals that showed gross evidence of infarction were excluded from the study. Schaper has shown that the anterior wall of the left ventricle, including the anterior papillary muscle, is supplied by the left anterior descending coronary artery, and the posterior wall, including the posterior papillary muscle, is supplied by the circumflex coronary artery.[6,9] In these experiments, since the left anterior descending coronary artery was occluded, the anterior papillary muscle region was supplied by collateral vessels developing from the circumflex coronary artery and was designated "collateralized myocardium." Transmural samples of left ventricular myocardium from the anterior wall, including the anterior papillary muscle, and the posterior wall, including the posterior papillary muscle, were obtained (fig. 3). Each sample then was divided into subendocardial, midmyocardial, and subepicardial portions and weighed. Radioactivity in tissue samples and reference arterial blood samples obtained during each microsphere injection was counted in a Packard® sodium iodide scintillation counter. Normalized regional blood flows were calculated per 100 g of myocardium,[10] and endocardial/epicardial (endo/epi) blood flow ratio was calculated for each region. Dogs in which transmural samples showed markedly diminished subendocardial blood flow (endo/epi ratio less than 0.5) during awake control measurements were excluded from subsequent analysis, as this was considered evidence of subendocardial infarction.

TACHYCARDIA-INDUCED ISCHEMIA EXPERIMENTS

In the second set of experiments, we wished to test the effect of halothane on collateral blood flow in the presence of myocardial ischemia. Pilot studies in eight dogs suggested that in order to produce reversible ischemia consistently, both the circumflex and right coronary arteries had to be occluded and pacing of the heart at rates greater than 180 beats/min had to be employed. Moderate tachycardia of 150–160 beats/min did not produce a reversal or reduction in endo/epi ratio in these animals.

The surgical preparation consisted of placing an Ameroid constrictor around the circumflex coronary artery and a left atrial catheter through a left thoracotomy, and then placing another Ameroid constrictor around the right coronary artery and pacing leads on the right atrium through a right thoracotomy (fig. 4). Recovery from surgery and laboratory training of dogs were as described above for the other experiments. In these dogs, with complete occlusions of the circumflex and right coronary arteries, the posterior wall of the left ventricle, including the posterior papillary muscle region, represented the collateralized myocardium.

Experiments were performed approximately 3 weeks after surgical preparation. Under sedation with xylazine, 5–15 mg intravenously, a 16-gauge catheter was inserted into the right femoral artery. Xylazine, an animal tranquilizer, produces bradycardia, which enabled atrial pacing using a Grass Instruments pulse generator. Occasionally, atropine 0.05–0.1 mg iv was administered to facilitate atrioventricular conduction and capture. With the dog sedated, but responsive to pain and breathing room air spontaneously, control hemodynamic and regional myocardial blood flow measurements were made

during atrial pacing at 90–110 beats/min. Then the heart was paced at approximately double the control rate (180–220 beats/min) for at least 5 min before hemodynamic and regional blood flow measurements were repeated. Pacing then was discontinued, halothane anesthesia was induced as described above, and the animal was ventilated mechanically. After approximately 1 h of stable halothane anesthesia (1% end-tidal), the heart again was paced at a rate similar to the control rate, and measurements were repeated. Final measurements were made in a few animals during halothane anesthesia and rapid atrial pacing.

At the end of the experiment, the animal was killed using potassium chloride injection, the heart was removed, and complete occlusions of both circumflex and right coronary arteries were confirmed by probing and visual inspection. Transmural samples from the anterior wall, including anterior papillary muscle, and posterior wall, including posterior papillary muscle, were processed as described above to yield endo/epi blood flow ratios. Exclusion criteria for infarctions and markedly diminished subendocardial blood flow during control measurement were followed as described above. Also, since it was our intention to produce ischemia, dogs that did not show at least a 50% reduction in endo/epi ratios in the posterior wall (collateralized region) during pacing at fast rates when compared with control endo/epi ratios were excluded from statistical analysis.

Statistical Analysis

Control values were tested for normality by constructing normal probability plots. Also, in the second group of experiments, since the outcome of pacing the heart at high rates during halothane anesthesia appeared to be bimodally distributed (three survivors and four deaths—see "Results," below), changes in mean arterial pressure, cardiac output, and endo/epi ratios during halothane–tachycardia state also were tested for normality by constructing normal probability plots. Data from both experiments were analyzed using Student's t test for paired values. Each dog served as its own control, and each measured hemodynamic value and endo/epi ratio was paired to the corresponding value during other interventions in the same dog and compared using Student's t test. Changes were considered significant when P was less than 0.05.

Results

Multiple Lesions Experiments

Of 15 dogs surgically prepared, four (27%) died during the first week of recovery. Among the remaining animals, two showed gross evidence of myocardial infarction at autopsy and were excluded from data analysis. In the remaining nine dogs, stenosis of the circumflex coronary artery was reproducible in only six dogs. Thus awake control measurements and measurements during halothane anesthesia were made in nine dogs, and measurements during stenosis were made in only six dogs.

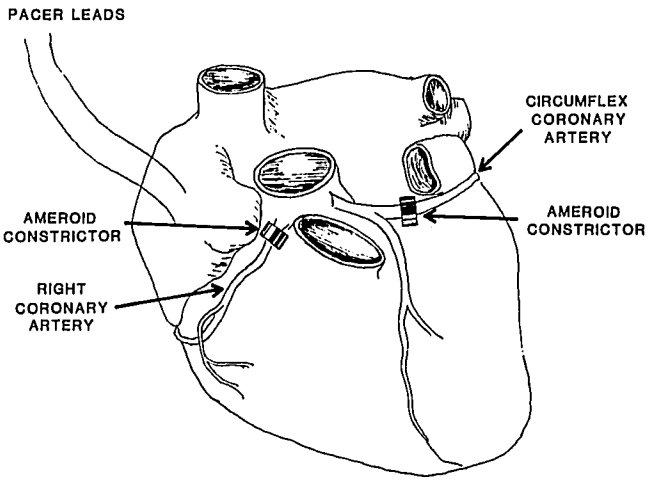

FIG. 4. Surgical preparation for tachycardia-induced ischemia experiments showing Ameroid constrictors on the circumflex coronary artery and right coronary artery and pacer leads on the right atrium.

Hemodynamic and arterial blood gas values are shown in table 1. Awake control measurements showed a hyperdynamic state with elevated resting levels of heart rate, mean arterial pressure, and cardiac output that all were distributed normally. During application of reversible stenosis of the circumflex coronary artery in the awake state, there were small but statistically significant decreases in heart rate and cardiac output. Halothane anesthesia significantly decreased heart rate, mean arterial pressure, and cardiac output. Application of stenosis during halothane anesthesia produced no further changes, but these values were still significantly different from awake measurements, with and without stenosis. With the exception of Pa_{O_2}, which was elevated markedly on induction of halothane anesthesia in oxygen, no other changes from awake control measurements were seen in blood gas values.

Regional myocardial blood flows (in $ml \cdot 100\ g^{-1} \cdot min^{-1}$) and endo/epi ratios for the normal region (posterior wall) and the collateralized region (anterior wall) are shown in table 2. During the awake control state, blood flow was significantly less in the collateralized region than in the normal region. However, there was no difference in the endo/epi ratios between these two regions at the same time. Reversible stenosis during the awake state produced only nonsignificant decreases in

TABLE 1. Hemodynamic and Blood Gas Data (mean ± SD). Multiple Lesions Experiments in Dogs with Occlusion of Left Anterior Descending Coronary Artery and Reversible Stenosis of Circumflex Coronary Artery

	Awake Control (N = 9)	Awake Stenosis* (N = 6)	Halothane (N = 9)	Halothane Stenosis* (N = 6)
Heart rate (beats/min)	115 ± 13	105 ± 15†	82 ± 17‡	84 ± 16‡§
Mean arterial pressure (mmHg)	117 ± 12	120 ± 21	88 ± 19‡	91 ± 22†¶
Left atrial pressure (mmHg)	2 ± 2	2 ± 2	5 ± 5	7 ± 5
Cardiac output (l/min)	6.01 ± 1.81	5.7 ± 1.37†	2.89 ± 0.68‡	3.31 ± 0.66†§
$F_{I_{O_2}}$	0.21	0.21	0.99	0.99
Pa_{O_2} (mmHg)	84 ± 8	86 ± 11	370 ± 60	390 ± 32
Pa_{CO_2} (mmHg)	28 ± 4	26 ± 3	28 ± 4	26 ± 4
pH_a	7.41 ± 0.03	7.41 ± 0.01	7.41 ± 0.03	7.42 ± 0.02

* Paired comparisons between awake control and halothane values were performed in only the six dogs.

† $P < 0.05$, ‡ $P < 0.01$ when compared with awake control values.
§ $P < 0.05$, ¶ $P < 0.01$ when compared with awake stenosis values.

blood flows and no changes in endo/epi ratios in the two regions. Halothane produced a significant 40–50% decrease in blood flows in both regions when compared with awake control measurements, but there was no significant difference between blood flows in the two regions. Endocardial/epicardial blood flow ratio was also unchanged during halothane anesthesia in both regions. Reapplication of stenosis during halothane anesthesia produced no further changes in blood flows or endo/epi ratios in the two regions.

TACHYCARDIA-INDUCED ISCHEMIA EXPERIMENTS

Nineteen dogs were surgically prepared, six (32%) of which died during the first 10 days of recovery. Experiments were performed on 13 dogs, but data from six dogs were excluded, since four of them showed no evidence of ischemia (50% reduction in endo/epi ratios) during tachycardia, and two showed gross evidence of infarcts in the posterior wall. Data from seven dogs are presented in tables 3 and 4.

Control values were normally distributed, and the hemodynamic values during the awake state (xylazine sedated) with pacing-induced tachycardia were no different than the awake control values. There was a small but significant decrease in Pa_{CO_2} and a small but significant increase in pH_a during the awake tachycardia state when compared with awake control values. Halothane produced an approximately 50% decrease in cardiac output but only a nonsignificant decrease in mean arterial pressure. Pacing at rates of 180–210 beats/min during halothane anesthesia produced severe decompensation in four dogs, two of which died before measurements could be made, and the other two died after measurements were made and pacing was discontinued. Only three of seven dogs tolerated tachycardia during halothane anesthesia well enough to recover once pacing was discontinued after measurements. However, in six of the seven dogs, there were decreases in mean arterial pressure during the halothane, tachycardia state.

Awake control values of blood flows in the normal (anterior wall) and collateralized (posterior wall) regions were similar. However, the endo/epi ratio in the collateralized region, though greater than unity, was signifi-

TABLE 2. Regional Myocardial Blood Flows and Endo/Epi Ratios (mean ± SD). Multiple Lesion Experiments in Dogs with Occlusion of Left Anterior Descending Coronary Artery and Reversible Stenosis of Circumflex Coronary Artery.

	Awake Control (N = 9)	Awake Stenosis* (N = 6)	Halothane (N = 9)	Halothane Stenosis* (N = 6)
Regional myocardial blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)				
Normal region (Posterior wall)	151 ± 74	133 ± 21	80 ± 24†‡	84 ± 22†§
Collateralized region (Anterior wall)	132 ± 77	121 ± 26	74 ± 24†§	80 ± 22†§
Significance of difference between normal vs collateral	$p < 0.05$	NS	NS	NS
Endo/epi ratios				
Normal region (posterior wall)	1.23 ± 0.23	1.17 ± 0.23	1.26 ± 0.21	1.3 ± 0.22
Collateralized region (anterior wall)	1.11 ± 0.35	1.21 ± 0.24	1.27 ± 0.2	1.22 ± 0.17
Significance of difference between normal *versus* collateral	NS	NS	NS	NS

NS = nonsignificant.
*Paired comparisons between awake control and halothane values were performed in only the six dogs.

† $P < 0.05$ when compared with awake control values.
‡ $P < 0.01$, § $P < 0.05$ when compared with awake stenosis values.

TABLE 3. Hemodynamic and Blood Gas Data (mean ± SD). Tachycardia-induced Ischemia Experiments in Dogs with Complete Occlusions of both Circumflex and Right Coronary Arteries

	Sedated Control (N = 7)	Sedated Tachycardia (N = 7)	Halothane (N = 7)	Halothane Tachycardia* (N = 5)
Heart rate (beats/min)	105 ± 7	200 ± 14	109 ± 13	193 ± 9
Mean arterial pressure (mmHg)	103 ± 15	95 ± 12	85 ± 16	61 ± 19
Left atrial pressure (mmHg)	4 ± 4	6 ± 5	8 ± 5	12 ± 8
Cardiac output (l/min)	3.47 ± 0.7	3.54 ± 1.2	1.71 ± 0.4†‡	1.6 ± 1.1
FI_{O_2}	0.21	0.21	0.99	0.99
Pa_{O_2} (mmHg)	84 ± 21	83 ± 26	336 ± 70	345 ± 134
Pa_{CO_2} (mmHg)	33 ± 5	30 ± 4§	32 ± 5	34 ± 7
pH_a	7.37 ± 0.03	7.40 ± 0.05§	7.34 ± 0.05	7.40 ± 0.12

* Paired comparisons between sedated control and sedated tachycardia and halothane values were performed in only the five dogs.

† $P < 0.01$, § $P < 0.05$ when compared with sedated control values.
‡ $P < 0.01$ when compared with sedated tachycardia values.

cantly less than in the normal region. During tachycardia in the awake animal, blood flow in the normal region was increased significantly by 90%, while in the collateralized region it showed only a nonsignificant increase. However, the endo/epi ratio during the awake tachycardia state was markedly decreased in the collateralized region, indicating severe underperfusion of the subendocardial layers. This was significantly different when compared with the normal region, where no changes in the endo/epi ratio were observed. During halothane anesthesia, blood flows in both regions were decreased significantly and the endo/epi ratio in the collateralized region was nearly restored to the control value. Pacing-induced tachycardia produced no further increases in blood flows in both regions but significantly decreased the endo/epi ratios in the normal as well as the collateralized regions in all the dogs. Per cent changes in mean arterial pressure, cardiac output, and endo/epi ratios in the normal as well as the collateralized region during the halothane tachycardia state were consistent with normal distribution.

Discussion

Gradual occlusion of a coronary artery using an Ameroid® constrictor is a well-established method to study coronary collateral circulation.[5-8] Myocardial infarction infrequently results, and resting blood flow and endo/epi ratio in the collateralized region are unchanged.[7,10,11] While there are anatomic differences between coronary collateral circulation in dogs and humans,[5,9] functional similarities exist. Nitroglycerin increases collateral blood flow in both dogs and humans,[6,12] and exercise-induced tachycardia decreases collateral blood flow and produces ischemia in dogs and humans.[10,11,13] Hence, the animal model we used bears resemblance to collateral circulation developing in humans as a result of gradual narrowing and occlusion of coronary arteries. The high incidence of mortality during recovery that we observed in the two experimental groups (27 and 32%, respectively) is similar to that reported by Schaper.[9,14] Schaper observed no evidence of infarction at autopsy in the dogs that died during

TABLE 4. Regional Myocardial Blood Flows and Endo/Epi Ratios (mean ± SD). Tachycardia-induced Ischemia Experiments in Dogs with Complete Occlusions of Both Circumflex and Right Coronary Arteries

	Sedated Control (N = 7)	Sedated Tachycardia (N = 7)	Halothane (N = 7)	Halothane Tachycardia* (N = 5)
Regional myocardial blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)				
Normal region (anterior wall)	153 ± 99	291 ± 221†	104 ± 56†‡	144 ± 34
Collateralized region (posterior wall)	163 ± 99	229 ± 161	91 ± 46†‡	120 ± 151
Significance of difference between normal *versus* collateral	NS	NS	NS	NS
Endo/epi ratios				
Normal region (anterior wall)	1.53 ± 0.33	1.40 ± 0.37	1.47 ± 0.2	0.90 ± 0.32†‡§
Collateralized region (posterior wall)	1.10 ± 0.12	0.47 ± 0.25¶	0.98 ± 0.32	0.31 ± 0.21¶**
Significance of difference between normal *versus* collateral	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$

NS = nonsignificant.
* Paired comparisons between sedated control and sedated tachycardia and halothane values were performed in only the five dogs.

† $P < 0.05$, ¶ $P < 0.01$ when compared with sedated control values.
‡ $P < 0.05$ when compared with sedated tachycardia values.
§ $P < 0.05$, ** $P < 0.01$ when compared with halothane values.

recovery and concluded that ventricular fibrillation due to ischemia was the cause of death.[14] We also performed autopsies on two dogs that died during recovery and found no histologic evidence of infarction.

Under normal conditions, blood flow in the subendocardial layers is slightly greater than in the subepicardial layers, so that endo/epi ratio is greater than one. But greater compressive forces, increased requirement for substrates, and decreased capacity for vasodilation in the subendocardium make it more vulnerable to ischemic injury.[15] Under experimental conditions, reversal of endo/epi ratio usually signifies hypoperfusion and ischemia of subendocardium.[10,11,15,16] Use of 15-μm microspheres for measurement of the endo/epi ratio has yielded values ranging from 1.27 to 1.5.[15] The values we obtained fell within this range. A threshold value of endo/epi ratio has not been established for ischemia. Under normal conditions, transmural differences in blood flow and metabolites are not greater than 10 to 20%.[15] When coronary blood flow is impaired, steep transmural gradients for blood flow, oxygen, and lactate develop.[15] Since a critical value for ischemia has not been established, we arbitrarily defined subendocardial ischemia as a 50% reduction in endo/epi ratio, indicating a reversal of the normal transmural gradient and underperfusion of the subendocardium. Control myocardial blood flow values that we obtained are 20–30% greater than frequently reported.[15] This could be attributed to the sedated but awake state, resulting in some excitement and a hyperdynamic circulation.

We administered halothane in oxygen, as is the common clinical practice. Arterial oxygen tension greater than 400 mmHg produces a 10% decrease in myocardial blood flow.[15] The reduction in myocardial blood flow that we observed during halothane could be attributed partly to increased arterial oxygen tension. To our knowledge, there is no evidence that high arterial oxygen tension affects endo/epi ratio.

Multiple Lesions Experiments

With chronic occlusion of the left anterior descending coronary artery, collateral vessels arise from the circumflex coronary artery to supply the anterior wall of the left ventricle, including the anterior papillary muscle. Though awake control values of myocardial blood flow were slightly but significantly less in the collateralized region, endo/epi ratios in both regions were normal. These findings agree with those reported earlier by others.[7,10,11] In applying a reversible stenosis to the circumflex coronary artery supplying the collateral circulation, it was our intention to simulate the clinical condition in humans in whom stenotic lesions frequently affect multiple vessels. The stenosis that we applied was presumably mild, since after an initial 10–15% reduction in flow, autoregulation resulted in vasodilation of the vascular bed distal to the stenosis and blood flow in the circumflex coronary artery was restored. The evidence for vasodilation distal to the stenosis is the transient hyperemic response observed on relieving the stenosis (fig. 2). Blood flow and the endo/epi ratio in the collateralized region during stenosis also were well maintained. Induction of anesthesia with halothane resulted in significant decreases in heart rate, mean arterial pressure, and cardiac output. Vatner and Smith[17] and Merin *et al.*[18] reported significant increases in heart rate during halothane anesthesia, but awake control heart rates in their well-trained animals were much lower than what we observed. Our dogs were somewhat hyperdynamic during awake control measurements, and in such an experimental preparation the effect of anesthetic agents would be exaggerated. This could perhaps explain the significant decreases in heart rate, mean arterial pressure, and cardiac output during the moderate dose (1% end-tidal) halothane anesthesia in our dogs. Halothane anesthesia also produced significant decreases in myocardial blood flow in our dogs. Similar findings have been reported by others.[17–19] The reduction in myocardial blood flow during halothane anesthesia is not indicative of ischemia, and it has been attributed to the diminished myocardial oxygen requirements due to reductions in blood pressure and myocardial contractility.[17–19] In spite of the reduction in perfusion pressure during halothane anesthesia, subendocardial blood flow was not affected adversely, as the endo/epi ratios in both regions remained unchanged. Even with reapplication of stenosis to the circumflex coronary artery during halothane anesthesia, and the resultant autoregulatory vasodilation distal to the stenosis, blood flows and the endo/epi ratios in both normal and collateralized regions remained unchanged. A more severe stenosis resulting in sustained reduction in blood flow might have produced a "steal phenomenon" in the collateralized region. However, Gould *et al.* have shown that to produce a sustained decrease in resting coronary flow, stenosis must be greater than 85%,[20] a degree of stenosis that we were hesitant to inflict in the presence of an already occluded left anterior descending coronary artery. We also must acknowledge that the applied stenosis during the awake state perhaps did not result in the same degree of luminal narrowing as the one applied during halothane anesthesia. Although stenosis applied each time was sufficient to produce a transient 10–15% decrease in blood flow, it must have required lesser encroachment on the cross-sectional area to produce the same effect during halothane anesthesia, due to the lower perfusion pressure. Also, the decrease in heart rate during halothane anesthesia and the resultant prolongation of diastolic duration might have augmented blood flow in the collateralized region. It is possible that

we might have observed a "steal phenomenon," had we maintained the heart rate at the control value during halothane anesthesia. Still, our data suggest that, unlike powerful coronary vasodilators such as lidoflazine and dypyridamole, which decrease collateral blood flow by producing a "steal phenomenon,"[6,21] halothane maintains collateral blood flow even in the presence of vasodilation induced by mild stenosis of the artery supplying the collateral bed. We conclude that coronary vasodilatory effect ascribed to halothane by Domenech must be minimal.[22]

Tachycardia-induced Ischemia Experiments

Our intent in these experiments was to study the effect of halothane on ischemic myocardium. Our hypothesis was that, since propranolol increases collateral blood flow during ischemia,[23,24] and halothane resembles propranolol in reducing infarct size,[25,26] halothane might have a beneficial effect on collateral blood flow during ischemia. In dogs with normal coronary arteries, an increase in heart rate to more than 200 beats/min does not decrease subendocardial blood flow, but with maximal coronary vasodilation, produced by adenosine and dypyridamole, tachycardia decreases the endo/epi ratios markedly.[27,28] In our experiments, the collateralized region exhibited characteristics of maximal vasodilation even in the awake but sedated animals, in that pacing-induced tachycardia produced marked reductions in the endo/epi ratios. Also, while there was no difference between myocardial blood flows to the normal and the collateralized regions during tachycardia in the awake but sedated animals, myocardial blood flow to the normal region was increased significantly when compared with control values, while an equivalent increase was not observed in the collateralized region. This suggests that the collateral circulation was not able to accommodate the increased demand for blood flow. Induction of halothane anesthesia did not produce significant reductions in mean arterial pressure, as it did in the first set of experiments, perhaps because we maintained the heart rate in these experiments by atrial pacing. As in the first set of experiments, halothane produced significant decreases in myocardial blood flows to both normal and collateralized regions and had no adverse effect on the collateral bed when the heart rate was maintained close to control values. However, tachycardia during halothane anesthesia did not produce an equivalent increase in myocardial blood flow, even to the normal region as seen during tachycardia in the awake state, perhaps due to the dramatic hemodynamic and left ventricular dysfunction that led to the demise of four of seven dogs. Although the decrease in the endo/epi ratio in the normal region resulting from tachycardia during halothane anesthesia was statistically significant, it may not represent subendocardial ischemia, since the value is close to unity, indicating near equal transmural blood flow. However, we speculate that this reduction and the marked decrease in the endo/epi ratio in the collateralized region, in combination with negative inotropic effects of halothane, might have contributed to the global ventricular dysfunction. Lowenstein *et al.* have reported that halothane produced a dose-dependent depression of function of a region of myocardium supplied by a narrowed coronary artery.[3] This depression was not observed in normal regions of the myocardium. They attributed this to ischemia due to reduction in blood flow in the narrowed coronary artery, resulting from the decrease in perfusion pressure produced by halothane.[3] While both increases in systolic pressure and heart rate increase myocardial oxygen consumption, Loeb *et al.* have shown that the stress of tachycardia results in "more myocardial ischemia than the stress of increased afterload."[29] It appears that the combination of reduced perfusion pressure produced by halothane and tachycardia resulted not only in further reductions in the endo/epi ratio in the collateralized region, but significant reductions in the normal region also. Combined with the negative inotropic effect of halothane, this might have led to ventricular dysfunction and circulatory collapse.

In interpreting our data, the following points have to be taken into account: 1) By eliminating dogs that showed evidence of infarction or decreased blood flow to the collateralized subendocardium at rest, we may have preselected dogs with well-developed collateral circulation that were unlikely to exhibit "steal phenomenon." Dogs with "immature" collateral circulation might have exhibited different findings with halothane. 2) Although we trained the dogs to lie quietly on their sides during the weeks of recovery from surgical preparation, control measurements in our first set of experiments showed evidence of hyperdynamic circulation. Therefore, for the tachycardia-induced ischemia experiments, we sedated the dogs using xylazine, which also produced bradycardia and enabled atrial pacing. The effect of xylazine on coronary circulation and its interaction with halothane is unknown. It is possible that some of the effects that we observed were due to xylazine–halothane interaction and not due to halothane alone. 3) In our statistical analysis, we made multiple comparisons for which we did not make corrections. However, for variables that showed marked changes, such as reductions in endo/epi ratio in collateralized regions during tachycardia without and with halothane, confidence intervals for 99% probability were narrow enough (−1.22 to −0.12) that multiple comparisons probably did not affect their levels of significance. 4) Finally, in applying these findings to humans, it has to be acknowledged that dogs develop an extensive collat-

eral vessel network, whereas in humans collateralization is not as extensive.[5,9] Thus, the protective role of the collateral circulation in humans may not be as great as in dogs. Drugs and interventions that do not decrease collateral blood flow in dogs might well do so in humans. Although there is prodigious literature on collateral circulation in humans, its functional significance continues to be debated.[12,30,31]

In conclusion, we found that in a canine model of well-developed coronary collateral circulation, halothane maintained blood flow to the collateralized subendocardium at normal heart rate (lower than control), despite reduced perfusion pressure. However, in dogs sedated with xylazine, ischemia induced in the collateralized region by tachycardia became worse during halothane and often led to severe ventricular dysfunction.

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