

Regional Blood Flow and Tissue Oxygen Pressures of the Collateral-Dependent Myocardium during Isoflurane Anesthesia in Dogs

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The authors investigated the effects of isoflurane on blood flow and tissue oxygen pressures of a collateral-dependent myocardium. Seventeen dogs divided into two groups were studied 3-4 weeks after implantation of ameroid coronary artery constrictors to completely occlude the proximal part of the left anterior descending artery. Experiments were performed during anesthesia with an opiate that was infused intravenously throughout the experiments. In Group 1 ($n = 9$), measurements were obtained during control and during isoflurane- (1.6-2.2 vol%) induced hypotension (mean arterial pressure, 60 mmHg). In Group 2 ($n = 8$), the identical protocol was applied, but norepinephrine was infused to maintain normotension. Dipyridamole effects were studied in five animals of Group 2 after a second control period at least 1 h after discontinuation of isoflurane. Isoflurane-induced hypotension caused reductions of blood flow and surface tissue oxygen pressures in the collateral flow-dependent area. Vasodilation in the normal left ventricular areas was demonstrated by an unchanged blood flow despite a reduced oxygen consumption and by a significantly increased coronary sinus hemoglobin oxygen saturation. When arterial pressure was maintained at its control level by norepinephrine, tissue oxygen pressures remained constant and collateral as well as normal area flow increased significantly during isoflurane. Coronary vascular resistance was lower during administration of isoflurane and norepinephrine compared with that during isoflurane induced hypotension, suggesting a significant contribution of tissue oxygen demand in regulation of coronary vascular resistance. At comparable levels of arterial pressure and left ventricular oxygen consumption, normal zone blood flow was significantly higher during dipyridamole than during isoflurane and norepinephrine. Thus, isoflurane-induced hypotension decreased blood flow and tissue oxygen pressures of collateral flow-dependent myocardial areas. However, neither isoflurane nor dipyridamole caused such alterations when arterial pressure was normal. (Key words: Anesthetics, intravenous; piritramid. Anesthetics, volatile; isoflurane. Heart: blood flow; collateral blood flow; dipyridamole; myocardial ischemia; perfusion pressure; tissue oxygen pressures. Measurement techniques: radioactive microspheres; tissue oxygen pressures.)

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ISOFLURANE IS KNOWN to produce coronary vasodilation in humans¹⁻³ as well as in several experimental animal models,⁴⁻⁷ uncoupling oxygen supply from myocardial metabolic demands.⁸ Simultaneously, isoflurane reduces myocardial oxygen consumption due to a decreased left ventricular afterload and to decreased inotropism.⁹⁻¹¹ Although an unchanged or even improved myocardial oxygen balance can be calculated from these effects for a normally supplied myocardium (which may also be inferred from an increased coronary venous P_{O_2} when isoflurane is administered), an improved oxygen balance may not necessarily apply to myocardial areas with a limited vascular reserve, e.g., a poststenotic or a collateral flow-dependent myocardium: Recent evidence by Priebe and Foëx¹² suggests that reduced myocardial oxygen utilization during isoflurane is outweighed by a reduced oxygen supply to the myocardium distal to a "critical" stenosis, leading to ischemia and dysfunction in the myocardium at risk. However, Tatekawa *et al.* found no evidence for myocardial ischemia, although blood flow through a stenotic coronary artery was diminished significantly by isoflurane.¹³

A more complex and perhaps clinically relevant question is whether isoflurane can induce "coronary steal." Inter coronary myocardial steal may occur in areas distal to a completely occluded coronary artery, wherein metabolic needs are supplied by collateral vessels originating from a coronary artery with a similarly restricted vascular reserve.¹⁴ A prerequisite for studies evaluating "coronary steal" is that coronary perfusion pressure is kept constant, because a reduced perfusion pressure might alter collateral flow by itself. There are two reports available that attempt to evaluate the capacity of isoflurane for producing coronary steal: Buffington *et al.* studied both blood flow to and segment function in a collateral-dependent myocardium and found that both were decreased with isoflurane, depending on the degree of blood flow restriction through the supplying coronary artery.¹⁵ How-

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ever, a problem of this study is that blood flow, instead of perfusion pressure, was maintained and that the collateral-dependent myocardium obviously had to already be severely ischemic at the beginning of the experimental steps when isoflurane caused a redistribution of blood flow. Thus, coronary steal cannot be inferred from these results without reservations. Cason *et al.*, in a canine preparation having the requirements for evaluating coronary steal as proposed by Becker,¹⁴ found no signs of coronary steal in the collateral supplied myocardium when coronary perfusion pressure was kept constant by aortic constriction.¹⁶

These two reports, as well as the work by Priebe and Foëx,¹² point out the importance of perfusion pressure when studying the potential for any agent to cause ischemia in a postsenotic or a collateral flow-dependent myocardium. To further confirm the importance of perfusion pressure, we studied the effects of isoflurane on blood supply and oxygen pressures of collateral flow-dependent myocardium of dogs at different perfusion pressures: In a first group of dogs, we tested isoflurane effects on collateral-supplied as well as normal myocardial areas when mean arterial pressure was lowered to 60 mmHg. In a second group, the hypotensive effects of isoflurane were counterbalanced by infusion of norepinephrine, thereby keeping arterial pressure close to its control level. Norepinephrine was used in this study to mimic the situation of a patient with a stress-induced catecholamine release during surgery. We furthermore studied the effects of dipyridamole to compare its vasodilatory potency with that of isoflurane at comparable levels of perfusion pressure and left ventricular oxygen consumption.

Methods

IMPLANTATION OF AMEROID CORONARY CONSTRICTORS

A total of 17 mongrel dogs of either sex had ameroid constrictors implanted around their left anterior descending (LAD) arteries to produce a collateral flow-dependent myocardium within 2–3 weeks. Mean body weight of all animals was 32.5 kg. The dogs were anesthetized with ketamine and flunitrazepam. Their tracheas were intubated and the lungs mechanically ventilated. Anesthesia was maintained with nitrous oxide and isoflurane (1–2 vol%). A thoracotomy was performed during sterile surgery in the fourth intercostal space. The pericardium was opened and the proximal LAD artery dissected free of surrounding connective tissue. Ameroid constrictors with an external diameter of 10 mm were slipped over the vessels. The internal diameter of the constrictors was chosen to be 10% smaller than the outer diameter of the LAD arteries to assure tight fit with the

vascular wall. The pericardium and the thoracic wall were closed and the dogs allowed to recover during the next 3–4 postoperative weeks. All experiments were approved by the Federal Animal Care Committee.

EXPERIMENTAL PREPARATION

At the date of the acute experiment, the afebrile and normal-behaving dogs were anesthetized with iv ketamine (8–10 mg/kg), flunitrazepam (0.1 mg/kg) and atropine (0.5 mg). After endotracheal intubation, mechanical ventilation was used to keep arterial P_{O_2} at 100 mmHg and end-expiratory CO_2 at 4.5 vol%. An opiate was infused intravenously throughout the experimental period (pir tramid, 1 mg \cdot kg⁻¹ \cdot h⁻¹, Janssen, Denmark). This infusion rate was chosen because it maintained stable and physiologic hemodynamic conditions in previous experiments.

Catheters were inserted into the abdominal aorta and in the pulmonary artery (7-Fr Swan-Ganz). Under fluoroscopic guidance, a double-tip manometer (Millar Instruments, Houston, Texas) was advanced into the left ventricular chamber for simultaneous determination of left ventricular and ascending aortic blood pressures. A polyethylene catheter was inserted into the coronary sinus through a jugular vein, and an 8-Fr Fogarty catheter was inserted into the inferior vena cava through a femoral vein. The pericardium was opened through a left thoracotomy in the same intercostal space that had been used for implantation of the ameroid constrictors. A catheter was inserted into the left atrium through its auricle for detection of left atrial pressure and for injection of radioactive microspheres.

Two highly flexible silicone rubber disks were then sutured onto the left ventricular surface with the use of four to five atraumatic sutures. These disks had a plastic ring mounted in their centers, which served as an electrode holder for the multichannel P_{O_2} surface electrodes. One of these electrode holders was placed on the left ventricular base on the territory supplied by the left circumflex artery, the second on the heart distal to the ameroid constrictor, next to the LAD artery. Control experiments and work by others indicated that collateral flow-dependent myocardium was most likely to be expected in this region.¹⁷

HEMODYNAMIC MEASUREMENTS

Left ventricular pressure, aortic pressure, pulmonary artery pressure, left atrial pressure, and ECG were continuously monitored. Cardiac output was determined as the mean of triplicate injections of 5 ml ice-cold saline (Gould SP 1425®, Statham Instruments, Oxnard, California). The maximal contractile element velocity (V_{max}) as an indicator of left ventricular contractility was calculated from the left ventricular pressure curves during the

isovolemic systole.^{18,19} Blood gas values, hemoglobin oxygen saturation, and oxygen content in arterial and coronary venous blood samples were derived from an ABL 3000® (Radiometer, Copenhagen, Denmark) and a CO-Oxymeter 282® (Instrumentation Laboratories, Lexington, MA), respectively. Left ventricular oxygen consumption was calculated by multiplying the arterial-coronary sinus oxygen content difference by total left ventricular blood flow. Coronary vascular resistance was obtained by dividing the mean arterial to left atrial pressure gradient by left ventricular blood flow.

DETERMINATION OF LEFT VENTRICULAR SURFACE OXYGEN TENSIONS

The measuring device consists of a Clark-type electrode²⁰ and has eight thin platinum cathodes and one Ag/AgCl anode incorporated. Details of the method have been described.^{21,22} In brief, at a constant polarization voltage of approximately -700 mV, a single platinum wire with a diameter of 15 μm registers a reduction current linearly dependent on the partial pressure of oxygen. The wires are randomly distributed on the electrode surface and measure oxygen pressures independent of each other. The radius of the oxygen-sensitive surface area of the platinum wires depends on the thickness of the membrane used and is 20–25 μm with a membrane of 25 μm .²¹ Because of the relatively high catchment area, the electrodes detect averaged oxygen pressures on small arteriolar or venular vessels, capillaries, and cardiac muscle cells. Both electrodes were calibrated in physiologic saline solutions equilibrated with pure nitrogen as well as 5% and 10% oxygen in nitrogen before and after each measurement on the heart. *In vitro* experiments had demonstrated that the reduction current of the electrode wires increased linearly in the calibrated range when P_{O_2} was increased in steps of 1%. We furthermore excluded any interference by isoflurane²³ with the electrode signals by equilibrating the calibration solutions with different concentrations of the anesthetic (0–3 vol%).

The reduction current signals of each of the eight wires are amplified, digitized, and processed with a PDP 11/23® computer (Digital Equipment Corporation, Maynard, Massachusetts). When placed in the holders on the left ventricular myocardium, the electrodes were suffused with 100% nitrogen and 100% oxygen for several minutes. Experiments were continued only if the recordings remained unchanged. This was necessary to exclude a diffusion of room air into the space between the electrode and the myocardium and a subsequent detection by the electrode. Five of the electrode holders required one to two additional sutures to prohibit gas diffusion to the electrode. It was then tested whether the LAD electrode had indeed been placed on the collateral flow zone. This was done by a brief inflation of the Fogarty catheter to decrease arterial pressure to about 50 mmHg, which was

followed by an increased heart rate. If the location of this electrode was correct, P_{O_2} recordings started to decrease within 1 min, whereas recordings of the circumflex electrode remained stable.²⁴ Three of the LAD electrodes had to be repositioned after this maneuver because they measured oxygen pressures of a normal myocardium or a border zone in their first position. Approximately 80 individual oxygen pressure measurements were collected at each step of the experiments. The distribution of these values is thought to reflect tissue oxygenation, giving the net result of nutritive blood flow and oxygen consumption.

DETERMINATION OF MYOCARDIAL BLOOD FLOW

The reference withdrawal method was applied to measure blood flow to the heart with radioactive microspheres.²⁵ Standard carbonized microspheres with a mean diameter of $15 \pm 0.9 \mu\text{m}$ were used (3-M Company, St. Paul, Minnesota). For each blood-flow determination, 4.0–5.0 million microspheres suspended in physiologic saline were injected over a period of 25–30 s through the left atrial catheter, which was subsequently flushed with 20 ml warmed saline. An arterial reference sample was withdrawn at a constant flow rate from the abdominal aorta. Withdrawal was started 20 s before the microsphere injection and was continued for 120 s thereafter.

The dogs were killed by injection of KCl at the end of the experiments and the hearts removed. The LAD arteries were excised together with the ameroid constrictors and complete occlusion verified by injection of saline with a pressure exceeding systolic arterial pressure. Leakage of fluid was observed in no experiment. The left ventricular myocardium including the septal wall was dissected into 180 tissue specimens of comparable size (endocardium, midwall layer, epicardium) following a standardized protocol. The perfusion territory of the LAD was considered to increase from the base to the apex of the left ventricular free wall.¹⁷ To ensure that myocardial tissue samples represented true collateral flow-dependent myocardium, only the tissue specimens from the center of this territory were considered during the subsequent calculation of collateral blood flow. Thus, the average weight of the collateral-dependent myocardium amounted to 15–20 g. Flows to the tissue samples were obtained by comparison with the activity found in the arterial reference samples. The total number of microspheres trapped and blood flow per gram tissue were determined in each individual sample. The relatively high number of microspheres injected assured that all tissue samples contained a minimum of 400 spheres.²⁶

EXPERIMENTAL PROTOCOL

The animals were randomly assigned to two groups and subjected to different experimental protocols. Each

protocol included a control period with stable hemodynamic parameters and surface P_{O_2} over at least 30 min and one period while isoflurane was administered: The animals of Group 1 ($n = 9$) received isoflurane at a concentration sufficient to reduce mean arterial pressure to 60 mmHg. The animals of Group 2 ($n = 8$) received an infusion of norepinephrine starting with the onset of isoflurane, where the infusion rate of norepinephrine ($1\text{--}5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was adjusted to maintain mean arterial pressure near control. Recordings were repeated after 30 min of stable conditions. Because it was not known in the animals of Group 2 what concentration of isoflurane would be required to reduce mean arterial pressure to 60 mmHg, the experimental protocol was designed so that the first animal of Group 2 received the end-expiratory isoflurane concentration of the first dog of Group 1 and so forth. Thus, the mean concentrations of isoflurane given (1.8 vol%), as well as the concentration ranges (1.6–2.2 vol%), were identical in both groups. And although it is not completely clear what expired isoflurane concentrations would in fact have decreased MAP to exactly 60 mmHg in Group 2, the narrow distribution of the isoflurane concentrations administered (SEM: 0.06 vol%) indicates that there was no major influence of isoflurane concentrations on the results.

End-expiratory concentrations of isoflurane were measured by a multigas analyzer (EMMA[®], Engström, Medical AB, Sweden), which had been zeroed immediately before addition of the anesthetic with the animals' expired air. The above-described sequence of experimental steps had been chosen because we could not exclude an irreversible damage of the preparations when isoflurane alone was the first experimental step. Therefore, no further experimental steps were performed with the animals of Group 1.

A third experimental group was formed, consisting of the animals of Group 2 that received dipyridamole (0.5 mg/kg) at least 1 h after all determinations during isoflurane and norepinephrine had been accomplished and when systemic hemodynamic parameters and myocardial tissue P_{O_2} were close to their control values. End-expiratory isoflurane concentrations were not detectably different from zero by the EMMA[®] at that time. Because of experimental difficulties and a varying availability of radioactive isotopes, this group consisted of only five animals. Recordings were repeated at 5–10 min after termination of dipyridamole infusion.

STATISTICAL ANALYSIS

For detection of significant intragroup differences, the Wilcoxon test (Group 1) and the Friedman rank analysis of variance (Group 2) were applied. Significant intergroup differences and differences between normal and collateral-dependent cardiac areas were detected by the Fisher-Pit-

TABLE 1. Hemodynamic Parameters in the Animals of Group 1 (Isoflurane Alone) ($n = 9$; $\bar{x} \pm \text{SEM}$)

	Control	Isoflurane
MAP (mmHg)	114 ± 7	$61 \pm 3^{*†‡}$
CO ($\text{l} \cdot \text{min}^{-1}$)	2.97 ± 0.23	$2.41 \pm 0.15^{†‡}$
HR (beats/min)	101 ± 8	99 ± 9
LAP (mmHg)	7.6 ± 0.8	6.8 ± 0.6
SVR ($\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$)	3111 ± 309	$1787 \pm 96^{*}$
V_{\max} (dl/dt)	3.85 ± 0.2	$2.90 \pm 0.22^{*†}$
art P_{O_2} (mmHg)	99 ± 2	105 ± 2
art $O_2\text{cont}$ (vol%)	13.8 ± 0.7	11.3 ± 0.5
cor $O_2\text{cont}$ (vol%)	5.9 ± 0.3	$6.6 \pm 0.5^{*†‡}$
cor $AVDO_2$ (vol%)	8.0 ± 0.6	$4.7 \pm 0.3^{*†‡}$
art $O_2\text{sat}$ (%)	93 ± 1	94 ± 0.7
cor $O_2\text{sat}$ (%)	40 ± 2	$52 \pm 3.5^{*†‡}$
LVO_2C ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	7.8 ± 0.5	$4.3 \pm 0.5^{*†‡}$
CVR ($\text{mmHg} \cdot \text{min} \cdot \text{ml}^{-1}$)	0.77 ± 0.06	$0.49 \pm 0.04^{*†‡}$

MAP = mean arterial pressure; CO = cardiac output; HR = heart rate; LAP = left atrial pressure; SVR = systemic vascular resistance; V_{\max} = maximal contractile element velocity; art P_{O_2} = arterial P_{O_2} ; art $O_2\text{cont}$ = oxygen content in arterial blood; cor $O_2\text{cont}$ = coronary venous oxygen content; cor $AVDO_2$ = arterial to coronary venous oxygen content difference; art $O_2\text{sat}$ = oxygen saturation in arterial blood; cor $O_2\text{sat}$ = oxygen saturation in coronary venous blood; LVO_2C = left ventricular oxygen consumption; CVR = coronary vascular resistance.

Mean values \pm SEM.

* $P < 0.05$ versus control.

† $P < 0.05$ versus isoflurane and norepinephrine.

‡ $P < 0.05$ versus dipyridamole.

man test. Test results were corrected for multiple comparisons if necessary. The P_{O_2} distribution curves were analyzed by their mean values as well as by the numbers of measurements in the lowest P_{O_2} classes because these appear to be most appropriate to assess oxygenation of tissue areas at risk. Therefore, numbers of measurements of 0 mmHg and measurements in the lowest P_{O_2} class (0–5 mmHg) of the left ventricular summary P_{O_2} histograms were analyzed by chi-square test. Mean values \pm SEM were calculated for all parameters. A P value less than 0.05 was considered statistically significant.

Results

ISOFLURANE ALONE

The reduction of mean arterial pressure from its initial mean value of 114 ± 7 mmHg to 61 ± 3 mmHg required end-tidal isoflurane concentrations ranging from 1.6 to 2.2 vol% (mean value, 1.8 vol%). At a nearly unchanged heart-rate, systemic vascular resistance, cardiac output, and V_{\max} decreased significantly by 43%, 19%, and 25%, respectively (table 1). Left atrial pressures were normal throughout the experiments.

Coronary sinus oxygen hemoglobin saturation increased from $40 \pm 2\%$ to $52 \pm 3.5\%$ ($P < 0.05$). Isoflurane significantly reduced the arterial to coronary venous oxygen content difference from 8.0 ± 0.6 to 4.7 ± 0.3 vol%, thereby increasing coronary venous oxygen content by

TABLE 2. Regional Myocardial Parameters in the Animals of Group 1 (Isoflurane) ($n = 9$; $\bar{x} \pm \text{SEM}$)

	Control	Isoflurane
MBF ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	1.02 ± 0.06	$0.95 \pm 0.09^{*+}$
MBF coll ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	0.76 ± 0.05	$0.48 \pm 0.07^{*+}$
coll:normal flow ratio	0.71 ± 0.05	$0.50 \pm 0.06^{*+}$
endo ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	1.06 ± 0.09	$0.94 \pm 0.08^{*+}$
endo coll ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	0.71 ± 0.07	$0.45 \pm 0.09^{*+}$
epi ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	1.04 ± 0.10	$0.97 \pm 0.11^{*+}$
epi coll ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	0.79 ± 0.07	$0.63 \pm 0.13^{*+}$
endo:epi	1.01 ± 0.05	1.01 ± 0.06
endo:epi coll	0.73 ± 0.11	$0.52 \pm 0.07^{*+}$
ptO ₂ (mmHg)	67 ± 4	54 ± 3
ptO ₂ coll (mmHg)	52 ± 7	$24 \pm 6^{*+}$

MBF = myocardial blood flow; MBF coll = collateral blood flow; endo = subendocardial flow; endo coll = subendocardial flow in the collateral flow-dependent zone; epi = subepicardial blood flow; epi coll = subepicardial flow in the collateral-supplied myocardium; endo:epi = endo:epi ratio; endo:epi coll = endo:epi ratio in the collateral-supplied zone; ptO₂ = surface tissue P_O₂ on the normal myocardium; ptO₂ = surface tissue P_O₂ on the collateral flow-dependent myocardium.

Mean values \pm SEM.

* $P < 0.05$ versus isoflurane and norepinephrine.

[†] $P < 0.05$ versus diprydamole.

[‡] $P < 0.05$ versus control.

12% ($P < 0.05$). Global left ventricular oxygen consumption was reduced significantly from 7.8 ± 0.5 to 4.3 ± 0.5 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ($P < 0.05$).

Regional left ventricular blood supply of the healthy and collateral flow-dependent myocardial areas was affected differently by isoflurane: Whereas blood supply to the circumflex area remained almost unchanged, transmural blood flow to the collateral flow-dependent myocardium decreased significantly from 76 ± 5 to 48 ± 7 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ (table 2). Blood flow in the collateral-dependent area (-37%) was redirected toward the epicardial layers (-20%), leading to a pronounced reduction of subendocardial blood flow (-37%) and a significantly decreased endo:epi ratio (-29%). Thus, blood flow and endo:epi ratio in the vulnerable collateral-dependent LAD myocardium were significantly less than the corresponding results of the circumflex zone.

Recordings of left ventricular surface tissue P_O₂ revealed a slightly lower P_O₂ on the collateral-supplied area during control conditions: mean values of the summary P_O₂ histograms were 67 ± 4 mmHg (circumflex zone) and 52 ± 7 mmHg (LAD zone), respectively. However, no P_O₂ values in the lower P_O₂ ranges were detected. The administration of isoflurane resulted in a slight and insignificant leftward shift, i.e., to lower P_O₂ values of the summary histogram on the circumflex area, whereas a significant leftward shift was detected on the collateral-supplied myocardium (fig. 1, table 2). The mean value of the histograms on the collateral flow-supplied zone decreased to 24 ± 6 mmHg. Numbers of low P_O₂ values in this region increased significantly to 19% (0–5 mmHg) and

8% (0 mmHg), indicating a deterioration of local tissue oxygenation. A close and significant correlation ($r = 0.95$; $P < 0.001$) was obtained for changes of surface tissue P_O₂ of the LAD zone with changes of collateral blood flow (fig. 2).

ISOFLURANE AND NOREPINEPHRINE

As indicated above, end-expiratory isoflurane concentrations were identical in this group and in Group 1. Essentially unchanged mean arterial pressures required infusion rates of norepinephrine between 1 and 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in these animals. As a result of tachyphylaxis, the infusion rates had to be almost doubled during this experimental step. Heart rhythm remained stable, and extrasystoles were not observed. Infusion of norepinephrine did not influence heart rate but significantly increased cardiac output ($+38\%$) and V_{max} ($+36\%$). Systemic vascular resistance decreased significantly by 29%; left atrial pressure remained unchanged (table 3).

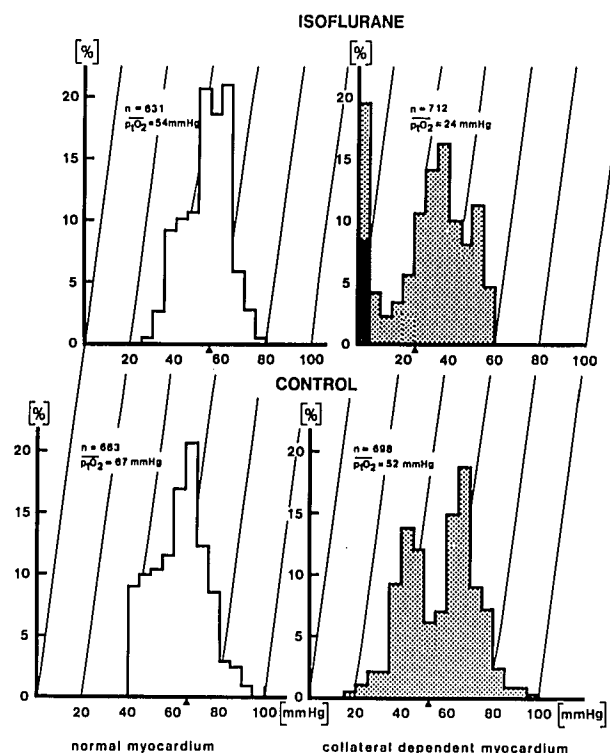


FIG. 1. Summary histograms of myocardial surface P_O₂ in the animals of Group 1 during control and during isoflurane at a mean arterial pressure of 60 mmHg. Histograms obtained on the normal myocardium and on the collateral flow-dependent zone are given. N denotes the absolute number of measuring points during each condition, P_O₂ the mean value of the summary histograms. A significant leftward shift of the distribution curve and an increased number of low P_O₂ values on the collateral-dependent heart are detected during isoflurane administration. Approximately 8% of all measurements were not detectably different from 0 mmHg (black bar).

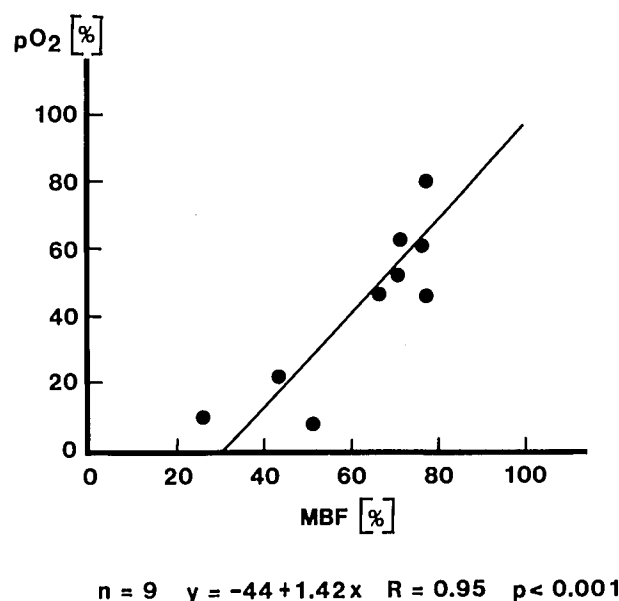


FIG. 2. Relationship between surface P_{O_2} and blood flow in the collateral flow-dependent myocardium during isoflurane. Points were obtained by comparison with the results of the normal zone and are expressed as percentage values. The significant correlation between both parameters indicates that the reduction in oxygen demand associated with isoflurane was outweighed by the reduction of collateral blood flow.

Blood flow values increased significantly in the collateral flow-dependent myocardium as well as in the normally supplied left ventricular areas (table 4): blood flow to the circumflex area increased by almost 116%, transmural blood flow through the collateral vessels, although significantly less, still by 66%. The endo:epi ratio remained unchanged in the healthy myocardium. A slight transmural redistribution of blood flow in the collateral flow-supplied myocardium was observed in favor of the subendocardial layers (0.75 ± 0.12 vs. 0.85 ± 0.15 ; NS). The endo:epi ratio in the collateral-dependent area significantly exceeded the endo:epi ratio of the animals that had been treated with isoflurane only. Changes in collateral blood flow during isoflurane plus norepinephrine were less pronounced than in the circumflex area because regional flow was significantly different between both areas during this experimental step.

The increase in myocardial blood flow was followed by equidirectional changes of coronary venous oxygen content (+64%) and coronary venous oxygen saturation (+52%), albeit left ventricular oxygen consumption was significantly increased. Coronary vascular resistance was significantly lower compared with that in dogs in Group 1.

Control values for tissue P_{O_2} were almost identical in this Group and in Group 1 (figs. 1, 3; tables 2, 4). The combination of isoflurane and norepinephrine maintained left ventricular tissue P_{O_2} histograms during isoflurane at

TABLE 3. Hemodynamic Parameters in the Animals of Group 2 (Isoflurane and Norepinephrine) ($n = 8$; $x \pm$ SEM)

	Control	Iso and Norepinephrine
MAP (mmHg)	111 ± 7	$99 \pm 3^*$
CO ($l \cdot min^{-1}$)	3.01 ± 0.17	$4.15 \pm 0.43^{*†}$
HR (beats/min)	107 ± 8	104 ± 6
LAP (mmHg)	7.9 ± 0.8	7.0 ± 0.8
SVR ($dyn \cdot s \cdot cm^{-5}$)	$2,942 \pm 282$	$2,077 \pm 319^{\dagger}$
V_{max} (dl/dt)	3.90 ± 0.2	$5.30 \pm 0.40^{*†}$
art P_{O_2} (mmHg)	99 ± 4	93 ± 3
art O_2 cont (vol%)	13.0 ± 0.8	13.8 ± 1.0
cor O_2 cont (vol%)	5.8 ± 0.4	$9.5 \pm 1.1^{*†\ddagger}$
cor AVDO ₂ (vol%)	7.2 ± 0.5	$4.4 \pm 0.3^{\dagger\ddagger}$
art O_2 sat (%)	94 ± 0.8	94 ± 0.6
cor O_2 sat (%)	44 ± 1.9	$67 \pm 2.0^{*†\ddagger}$
LVO ₂ C ($ml \cdot min^{-1} \cdot 100 g^{-1}$)	7.05 ± 0.4	$10.36 \pm 1.00^{*†}$
CVR ($mmHg \cdot min^{-1} \cdot ml^{-1}$)	0.73 ± 0.07	$0.33 \pm 0.09^{*†\ddagger}$

See table 1 for abbreviations. Mean values \pm SEM.

* $P < 0.05$ versus isoflurane.

† $P < 0.05$ versus control.

‡ $P < 0.05$ versus dipyridamole.

approximately 60 mmHg (collateral supplied area) and 63 mmHg (circumflex area). No low P_{O_2} values were detected (Fig. 3). Therefore, the mean value of the LAD area distribution curve as well as the numbers of low P_{O_2} values (0 mmHg and 0–5 mmHg) were significantly different between Groups 1 and 2.

DIPYRIDAMOLE

No statistically significant differences were detected between the two control periods encompassing the experimental step with isoflurane and norepinephrine. Mean arterial pressure decreased and heart rate increased after the infusion of dipyridamole. However, these changes did not reach the level required for statistical significance. Cardiac output was significantly increased (+45%), and systemic vascular resistance significantly decreased (–43%; table 5).

TABLE 4. Regional Myocardial Parameters in the Animals of Group 2 (Isoflurane and Norepinephrine) ($n = 8$; $x \pm$ SEM)

	Control	Iso and Norepinephrine
MBF ($ml \cdot min^{-1} \cdot g^{-1}$)	1.22 ± 0.10	$2.63 \pm 0.26^{*†\ddagger}$
MBF coll ($ml \cdot min^{-1} \cdot g^{-1}$)	0.86 ± 0.07	$1.43 \pm 0.27^{*†\ddagger}$
Endo:epi flow ratio	0.72 ± 0.05	$0.56 \pm 0.09^{*†}$
Endo ($ml \cdot min^{-1} \cdot g^{-1}$)	1.22 ± 0.08	$2.60 \pm 0.31^{*†}$
Endo coll ($ml \cdot min^{-1} \cdot g^{-1}$)	0.84 ± 0.07	$1.48 \pm 0.29^{*†}$
Epi ($ml \cdot min^{-1} \cdot g^{-1}$)	1.27 ± 0.15	$2.65 \pm 0.18^{*†}$
Epi coll ($ml \cdot min^{-1} \cdot g^{-1}$)	0.95 ± 0.11	$1.30 \pm 0.20^{*†\ddagger}$
Endo:epi	1.01 ± 0.06	0.96 ± 0.05
Endo:epi coll	0.75 ± 0.12	$0.85 \pm 0.15^{\dagger}$
pt O_2 (mmHg)	65 ± 4	63 ± 2
pt O_2 coll (mmHg)	51 ± 6	$60 \pm 6^{\dagger}$

See table 2 for abbreviations. Mean values \pm SEM.

* $P < 0.05$ versus control.

† $P < 0.05$ versus isoflurane.

‡ $P < 0.05$ versus dipyridamole.

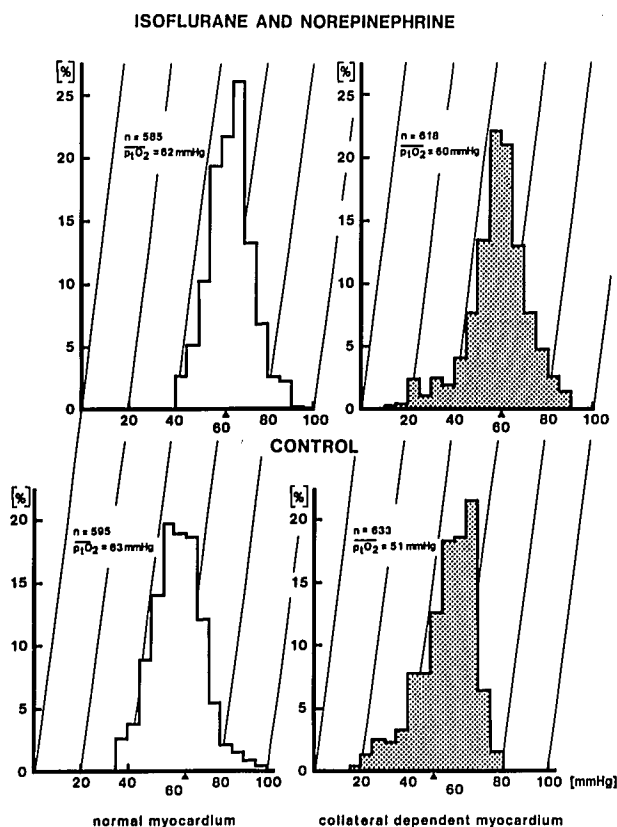


FIG. 3. Summary epicardial P_{O_2} distribution curves in the animals of the second group. The control step and the experimental step with isoflurane and norepinephrine are given. No major changes of shape or mean value were detected on both cardiac areas, indicating well-maintained tissue oxygen supply. For abbreviations see legend to figure 1.

Microsphere blood flow increased almost threefold in the healthy myocardium and was almost doubled in the collateral flow-dependent zone (table 6). The endo:epi

TABLE 5. Hemodynamic Parameters during Dipyridamole ($n = 5$; $\bar{x} \pm \text{SEM}$)

	Control	Dipyridamole
MAP (mmHg)	111 ± 5	$95 \pm 12^*$
CO ($\text{l} \cdot \text{min}^{-1}$)	3.21 ± 0.27	$4.66 \pm 0.41^{*†}$
HR (beats/min)	94 ± 6	113 ± 12
LAP (mmHg)	7.8 ± 0.9	10.0 ± 1.5
SVR ($\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$)	$2,733 \pm 109$	$1,563 \pm 290^†$
art P_{O_2} (mmHg)	97 ± 4	108 ± 5
art $O_2\text{cont}$ (vol%)	14.5 ± 0.61	13.8 ± 1.1
cor $O_2\text{cont}$ (vol%)	6.4 ± 0.3	$11.3 \pm 1.5^{*†‡}$
cor AVDO_2 (vol%)	8.1 ± 0.7	$2.4 \pm 0.5^{*†‡}$
art $O_2\text{sat}$ (%)	94 ± 0.6	95 ± 0.3
cor $O_2\text{sat}$ (%)	41 ± 2.6	$77 \pm 4.1^{*†‡}$
LVO_2C ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	7.2 ± 0.4	$8.2 \pm 0.7^*$
CVR ($\text{mmHg} \cdot \text{min} \cdot \text{ml}^{-1}$)	0.86 ± 0.09	$0.22 \pm 0.05^{*†‡}$

See table 1 for abbreviations. Mean values $\pm \text{SEM}$.

* $P < 0.05$ versus isoflurane.

† $P < 0.05$ versus control.

‡ $P < 0.05$ versus isoflurane and norepinephrine.

ratio remained unchanged in the collateral flow-supplied myocardium as well as in the circumflex area. The extraordinary vasodilatory potency of dipyridamole is reflected by significantly higher transmural blood flow values and a lower coronary vascular resistance when compared with the animals receiving either isoflurane alone or isoflurane plus norepinephrine. Also, coronary sinus oxygen content and oxygen hemoglobin saturation significantly exceeded the results obtained in the other groups (table 5). The arterial to coronary sinus oxygen content difference ($2.4 \pm 0.5 \text{ vol}\%$) was smallest during dipyridamole.

Surface tissue P_{O_2} decreased slightly on the circumflex-area as well as on the collateral-supplied myocardium. However, no low P_{O_2} values ($0-5 \text{ mmHg}$) were measured (fig. 4).

Discussion

The results of this study indicate that the administration of isoflurane at a concentration that decreased mean arterial pressure to 60 mmHg decreased tissue oxygen pressures and blood supply of the collateral flow-dependent myocardium. However, these effects were not directly related to coronary dilation caused by isoflurane because tissue oxygen pressures remained constant despite an increase in myocardial oxygen consumption when norepinephrine was infused together with isoflurane administration. The adverse effects observed during isoflurane alone, therefore, appear to result from the lower perfusion pressure and a subsequent reduction of blood flow and oxygen supply to the collateral-supplied myocardium.

ISOFLURANE ALONE, GROUP 1

The reduction of arterial pressure by isoflurane was followed by decreased surface tissue P_{O_2} and blood flow to the collateral-dependent myocardium. The leftward shift of the P_{O_2} distribution curve indicates that collateral flow was not sufficient during isoflurane administration to meet the, presumably reduced, metabolic demands of the collateral-dependent zone.

Decreased tissue oxygen pressures in the collateral-dependent myocardium during isoflurane are in accord with two recent studies, wherein isoflurane effects on myocardial areas at risk were studied. Buffington *et al.*¹⁵ stepwise reduced circumflex artery flow, and hence collateral perfusion pressure, and measured blood supply and regional myocardial function. Although the aim of their study and the experimental preparations are different from ours, their results agree with this study in as much as the reduced collateral perfusion pressure (which Buffington *et al.* measured as a reduction of blood pressure at the tip of the perfusion cannula and which we produced by lowering systemic arterial pressure) was followed by deterioration of regional function or tissue oxygenation, re-

spectively. Priebe and Foex¹² reported regional myocardial dysfunction of the poststenotic canine myocardium when arterial pressure was reduced by isoflurane. Recently, Tatekawa *et al.*¹³ reported a reduced perfusion of a poststenotic myocardium during isoflurane. However, these authors found no evidence of ischemia because regional function decreased comparably in poststenotic and normal areas. A problem of this study is that stenotic blood flow with isoflurane was still high and deteriorations in regional wall thickening occurred only at much lower perfusion rates in other studies.^{27,28} It therefore appears appropriate to conclude that the negative effects of a reduced poststenotic or collateral perfusion commonly outweigh the decreased oxygen demand after isoflurane administration.

Whether or not isoflurane worsened the degree of flow maldistribution cannot be answered because no measurements were made at a mean arterial pressure of 60 mmHg in the absence of isoflurane. Such an experimental step was not included because reduction of arterial pressure without isoflurane (*e.g.*, by use of the Fogarty catheter) in pilot experiments was always associated with changes in heart rate and left ventricular filling pressure, thereby prohibiting comparisons with isoflurane effects.

The reduction of collateral flow during isoflurane resulted from a reduced perfusion pressure at the origin of the collateral vessels and an absent or at least limited capacity for dilation. As discussed later, the experiments were designed to mimic the situation of patients with one coronary artery occluded but the other vessels intact and an asymptomatic heart at rest. In these patients, a reduced collateral oxygen supply by isoflurane-induced hypotension would endanger myocardial tissue oxygenation.

ISOFLURANE AND NOREPINEPHRINE, GROUP 2

To our knowledge, there are two reports available at present, referring to isoflurane effects on a collateral flow-supplied myocardium at an unchanged coronary perfusion pressure. Cason *et al.*¹⁶ studied blood flow and perfusion pressures of a collateral-supplied myocardium. Their experimental preparation is slightly different from ours because their preparations had an additional stenosis of a coronary artery to exhaust the vascular reserve of the healthy myocardium in order to study the capacity of isoflurane for producing "myocardial steal." Additionally, perfusion pressure was held constant by compression of the aorta. Based upon unchanged distal coronary artery pressures and collateral blood flow, these authors found no evidence for coronary steal.

Although not designed to investigate coronary steal, the results of this study correspond with these findings in that at a constant perfusion pressure collateral blood flow was not decreased by isoflurane. Collateral flow was even increased significantly in our animals. We assume that this increase is the result of the vasodilation produced by

TABLE 6. Regional Myocardial Parameters during Dipyrindamole (n = 5; x ± SEM)

	Control	Dipyrindamole
MBF (ml · min ⁻¹ · g ⁻¹)	1.07 ± 0.10	3.00 ± 0.50*†‡
MBF coll (ml · min ⁻¹ · g ⁻¹)	0.72 ± 0.08	1.50 ± 0.25*†‡
Coll:normal flow ratio	0.74 ± 0.06	0.50 ± 0.08*
Endo (ml · min ⁻¹ · g ⁻¹)	1.15 ± 0.13	2.89 ± 0.54*†
Endo coll (ml · min ⁻¹ · g ⁻¹)	0.69 ± 0.11	1.38 ± 0.36*†
Epi (ml · min ⁻¹ · g ⁻¹)	1.13 ± 0.16	3.02 ± 0.52*†
Epi coll (ml · min ⁻¹ · g ⁻¹)	0.61 ± 0.03	1.70 ± 0.30*†‡
Endo:epi	1.00 ± 0.04	0.96 ± 0.02
Endo:epi coll	0.75 ± 0.20	0.81 ± 0.21
ptO ₂ (mmHg)	62 ± 6	56 ± 5
ptO ₂ coll (mmHg)	63 ± 5	44 ± 6

See table 2 for abbreviations. Mean values ± SEM.

* P < 0.05 versus control.

† P < 0.05 versus isoflurane.

‡ P < 0.05 versus isoflurane and norepinephrine.

isoflurane in the circumflex territory together with a higher intravascular pressure at the microcirculatory level where the collateral vessels originate, *i.e.*, at arterioles or precapillary vessels.²⁹

However, in the experiments performed by Cason *et al.*, isoflurane was not a coronary vasodilator in the normal

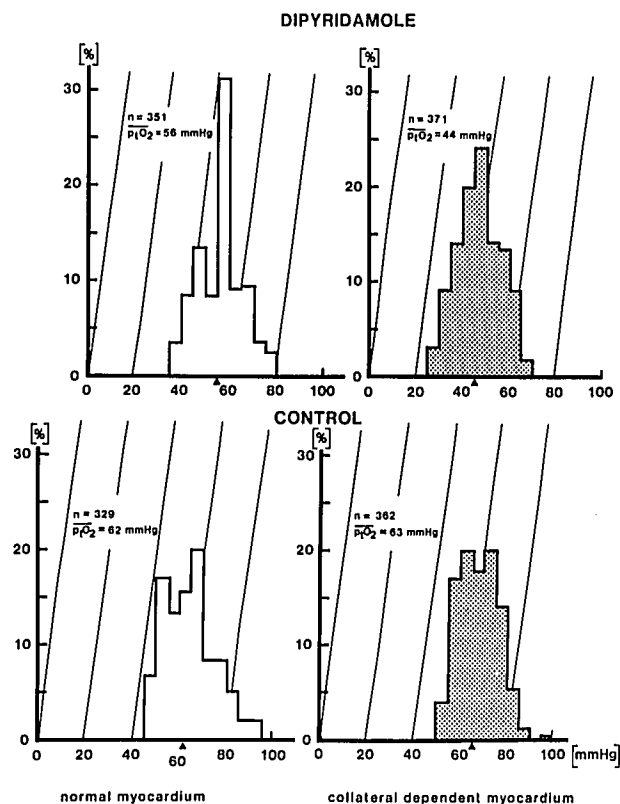


FIG. 4. PO₂ distribution curves during control and dipyrindamole. A slight leftward shift of the histograms is visible on both myocardial areas during dipyrindamole. However, no low PO₂ values were detected. For abbreviations see legend to figure 1.

myocardium and hence did not have the potential for producing coronary steal. This divergent finding might be explained by considerably higher concentrations of isoflurane administered in this study and/or divergent influences on left ventricular oxygen consumption: Although Cason *et al.* do not report their absolute isoflurane concentrations, we assume that the fentanyl-corrected MAC values were applied (1.5 MAC = 0.8–0.9 vol%); norepinephrine infusion in our study significantly increased myocardial oxygen consumption, whereas oxygen consumption was constant when MAP was maintained by aortic compression.

The capacity of isoflurane for producing coronary steal was also studied by Buffington *et al.*¹⁵ These authors studied normal and collateral myocardium blood flow distributions at different levels of normal zone flow and observed a redistribution of flow in favor of the nonischemic myocardium. As already discussed elsewhere,¹⁶ isoflurane produced coronary steal and a deterioration of regional myocardial function only when superimposed upon an already ischemic and dysfunctional heart. Only a tendency for blood flow redistribution was observed at the highest flow level ("full flow" or "autoregulated level"). Besides evident differences in the ischemic state of the myocardium, a second explanation for the divergent findings of Cason *et al.* and Buffington *et al.* may be that, as in the present study, left ventricular oxygen consumption contributed differently to the results. Therefore, isoflurane may prove a more potent coronary vasodilator if superimposed upon almost unchanged¹⁵ or even increased cardiac metabolic demands (this study), for example, during intraoperative stress-induced catecholamine release.

The impact of myocardial oxygen consumption on coronary vascular tone is also supported by the changes in coronary vascular resistance (CVR), which was significantly lower in the animals receiving isoflurane and norepinephrine as compared with dogs in Group 1. The low CVR in the norepinephrine group, therefore, appears to result from both the vasodilatory effects of isoflurane as well as from increased metabolic demands of the myocardium. In the study of Tatekawa *et al.*,¹³ normal zone blood flow also increased significantly when arterial pressure and left ventricular oxygen consumption were increased by phenylephrine.

DIPYRIDAMOLE

Dipyridamole was administered to evaluate the relative potency of isoflurane in comparison with one of the most potent coronary vasodilators known. Dipyridamole increased collateral and normal myocardial blood flows significantly more than the combination of isoflurane and norepinephrine. Influences of global cardiac parameters were minimal because mean arterial pressure was almost

identical in both steps, and left ventricular oxygen consumption was even slightly less during dipyridamole.

Buffington *et al.*¹⁵ report a significant improvement of collateral myocardial function in their second protocol with adenosine, when poststenotic coronary artery pressure was kept constant at 90 mmHg. Unfortunately, the authors do not provide data of collateral flow or the collateral:normal flow ratio during these conditions. However, it appears appropriate to infer that such an improvement in function should occur in combination with an improved blood flow.^{27,28} Thus, under the conditions of an unchanged perfusion pressure in a large coronary artery, the application of dipyridamole was supposedly beneficial rather than deleterious for collateral blood flow under both experimental protocols. Coronary steal was not observed in this study because additional stenosis of the circumflex artery was absent.¹⁴

The question arises why the almost threefold increase in normal zone blood flow was not followed by improved tissue oxygen pressures. As mentioned earlier, a significant and close relationship between tissue P_{O_2} and collateral flow was obtained in the animals of the first group. However, no significant correlations were obtained under the conditions of an increased blood flow. At present, our explanation is that excess oxygen passes through the myocardial microcirculation *via* functional shunt vessels³⁰ or *via* a diffusional shunt.^{31,32} The final reason for this discrepancy, however, is not fully understood at this time and remains the subject of further studies.

Regional blood flow to the normal zone during dipyridamole increased threefold and hence somewhat less than in other studies. This may be caused by incomplete vasodilation resulting from the relatively small amount of dipyridamole given or by the fact that the patent circumflex artery became flow limiting not only to perfusion of collateral-dependent areas.³³ This does not diminish the significance of the results, because the differences in blood flow can be expected to be even higher between dipyridamole and isoflurane at a comparable perfusion pressure.

METHODOLOGIC REMARKS

The dog preparation was considered appropriate, because collateral flow-dependent myocardial areas can be readily produced within a few weeks. Extrapolation of the results to humans depends on the validity of the canine collateral network as a model of human coronary artery disease. In contrast to those in humans, collateral vessels are largely located in the subepicardial canine myocardium and develop rapidly during the progress of coronary occlusion without producing myocardial infarction in a high percentage of the animals.²⁴ In accord with this, no signs of obvious myocardial infarction (abnormal wall movement, low epicardial tissue P_{O_2} or blood flow at con-

trol) were observed. The rapid development of the canine collateral network requires that investigations be performed as soon as possible after complete occlusion of the ameroid constrictors. *In vitro* experiments with the ameroid material provided evidence that most of the vessels were occluded at 2 weeks after implantation.

Collateral blood flow and tissue P_{O_2} at the time of the acute experiments were slightly below the values obtained in the healthy zone. Thus, oxygen supply of the collateral flow-dependent myocardium was slightly limited during control conditions. This situation most likely reflects a patient with an asymptomatic heart at rest but in whom signs of ischemia develop during exercise-increased metabolic demands or result from a decreased coronary perfusion pressure.

Transmural collateral blood flow as well as surface tissue oxygen pressures were decreased during isoflurane. Determinations of transmural myocardial oxygen tensions with needle electrodes suggested a lower tissue P_{O_2} in the subendocardium as compared with the subepicardium.^{34,35} Data of surface electrodes certainly do not represent subendocardial tissue P_{O_2} . However, the results obtained by needle electrodes suggest that transmural changes can be predicted by measuring epicardial P_{O_2} in combination with regional blood flow.^{34,36,37}

All experiments were carried out during anesthesia with a long-acting opiate, and all animals received ketamine, flunitrazepam, and atropine for induction of anesthesia. Anesthetized preparations were necessary mainly because a thoracotomy had to be performed in order to place the P_{O_2} electrodes on the left ventricular surface. The anesthetic regimen was identical in all animals, thereby minimizing differences between the experimental groups. At present, no reports are available concerning effects of piritramid on the myocardial circulation. We assume that such effects—similar to the effects of other narcotics—if present, are small.^{38,39} This can also be deduced from systemic or coronary hemodynamic control values that were similar to those reported in comparable studies.^{12,16} Nonetheless, an unchanged heart rate during application of isoflurane is most likely explained by the presence of an opiate.⁴⁰ Therefore, because of the superimposed negative inotropic effect of isoflurane, stroke volume and cardiac output decreased in the animals in Group 1.

In the animals of Group 2, norepinephrine was administered to keep arterial pressure at its baseline value. This was done to mimic the clinical situation of intraoperative stress with a relatively high myocardial oxygen consumption. The question is whether norepinephrine by itself or in combination with isoflurane could have improved the situation of the collateral flow-dependent myocardium. Norepinephrine, as a rather selective α_1 and β_1 agonist,⁴¹ increases myocardial contractility and acts as a

vasoconstrictor largely in the vascular periphery. One would expect that if there were effects on the coronary vasculature, norepinephrine would increase coronary vascular tone. However, this was not observed: Because of the increased metabolic demands, coronary vascular resistance was even significantly lower in the animals of Group 2 when compared with the first group. Because there is no evidence that norepinephrine has the potential to reduce the vascular tone of immature collateral vessels,⁴² the increase in blood supply to the collateral flow-dependent heart appears to result from the vasodilatory properties of isoflurane combined with the blood pressure augmentation at the origin of the collateral vessels by norepinephrine. Certainly, a contribution of a normally behaving border zone or a reactivity of the collateral vessels to metabolic stimuli during norepinephrine cannot be excluded. A further possibility that might explain an increased collateral blood flow in animals in Group 2 is that isoflurane reduced extravascular compressive forces. However, this is unlikely because indicators of these forces such as maximum coronary conductance, vascular reserve, or zero-flow pressure were not affected significantly by isoflurane.⁴³

In summary, blood supply and oxygenation of collateral flow-dependent myocardial areas were significantly decreased if perfusion pressure decreased to 60 mmHg with administration of isoflurane. In contrast, tissue oxygen pressures of the collateral flow-dependent myocardium remained unchanged and blood flow was even increased when arterial pressure was held constant. These results do not exclude that isoflurane has the potential to induce coronary steal because our experimental protocol was not designed to investigate this phenomenon. Rather, we studied the role of arterial pressure on a collateral flow-supplied myocardium with the other coronary arteries intact. Under the conditions of our study, the arterial pressure decrease played a pivotal role for the partially negative effects of isoflurane.

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