

Coronary Vascular Resistance during Halothane Anesthesia

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To study the effect of halothane on the coronary circulation, the circumflex diastolic coronary vascular resistance was measured in the working heart and total mean coronary resistance (TCR) in the isolated nonworking heart of the dog during administration of 100 per cent oxygen and during administration of 2-3 per cent halothane in oxygen. In the working heart, when the diastolic aortic pressure was kept at a nearly control level, halothane induced decreases of 12 per cent in circumflex diastolic coronary vascular resistance and 18 per cent in left ventricular arteriovenous oxygen content difference and no significant change in diastolic coronary blood flow. This effect occurred in spite of the absence of any significant change of myocardial oxygen consumption. In the nonworking beating, arrested or fibrillating heart, halothane induced a decrease of 24 per cent in total mean coronary resistance. Since the decrease in circumflex diastolic coronary vascular resistance in the working heart cannot be attributed to myocardial hypoxia and since the results in the isolated nonworking heart eliminate the influences of mechanical and neurohumoral factors on coronary resistance, it is concluded that the observed decrease in resistance is probably due to vasodilation produced by a direct action of halothane on the coronary vessels. This effect was not modified by beta-adrenergic blockade. (Key words: Heart, blood flow, myocardial; Heart, oxygen consumption; Anesthetics, volatile, halothane.)

THE EFFECT OF HALOTHANE on coronary blood flow regulation is not clear. Some investigators have reported that halothane decreases coronary blood flow in the same proportion that it decreases the oxygen demand of the heart and that halothane has no direct action on the coronary vessels.^{1,2} Other investigators have reported either an increase³ or a decrease⁴ in coronary resistance during high concentrations of halothane in the inspired air or end-tidal volume.

Difficulties in interpretation of the results of previous studies arise due to the possibility that changes in the metabolic and mechanical variables that influence coronary vascular resistance may be the result of the decreases in contractility and afterload of the heart produced by halothane,^{2,4-8} not due to direct effects of halothane on the coronary

vasculature. We have analyzed the direct and indirect actions of halothane on the coronary vascular resistance by studying its effects in the working and in the nonworking canine heart preparation.

Material and Methods

Two preparations in the dog were used.

WORKING HEART PREPARATION

Twenty-five mongrel dogs weighing between 18 and 25 kg were anesthetized by intravenous administration of thiopental in amounts just adequate to abolish the palpebral reflex. Subsequent small doses were administered as needed to perform the surgical procedure. The average total dose was 17.3 mg/kg. The lungs were ventilated with room air by means of a pump and an endotracheal tube and the thorax was opened at the level of the fourth intercostal space. An electromagnetic flow transducer of the cuff type (Biotronex Laboratory) was implanted around the circumflex coronary artery and a plastic snare was placed distal to it in order to obtain zero-flow recordings by short occlusions. A polyethylene catheter was placed in the ascending aorta through a brachial or femoral artery for pressure recording. In nine of the dogs, thin catheters were also placed in the main coronary vein through the coronary sinus and in the thoracic aorta to obtain simultaneous blood samples for the analysis of oxygen content. Aortic pressure was measured with an electronic transducer (Statham P23 Db). Coronary blood flow and aortic pressure were recorded on a physiograph (Gilson Medical Electronics). The oxygen content of the blood was measured by the Van Slyke manometer technique. Although the use of this technique for samples containing halothane results in falsely high values of oxygen content,⁹ the error is very small (less than 1 per cent for an oxygen content of about 18 ml/100 ml, in a sample equilibrated with 2 per cent halothane¹⁰ and would not affect our conclusions). The oxygen content of the blood obtained from the main coronary vein was assumed to represent mainly the venous oxygen content of the blood draining from the left ventricular wall. The oxygen consumption of that region of the left ventricular wall irrigated by the circumflex coronary artery was computed as the product of circumflex coronary blood flow, as measured with the electromagnetic flowmeter, times the difference in oxygen content between the aortic blood and the blood from the main coronary vein. For simplicity, this oxygen consumption is referred to as left ventricular oxygen consumption. The electromagnetic flowmeter was calibrated *in vitro* with blood (hematocrit 40 per cent). Diastolic

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coronary vascular resistance was computed as the ratio of late diastolic aortic pressure to maximal diastolic coronary flow.

After completion of the surgical procedure, the lungs were ventilated with 100 per cent oxygen. After stabilization of coronary blood flow and aortic pressure, a halothane vaporizer (Fluotec) was connected in series in the respiratory line. In this way, halothane was given with oxygen until a decrease of about 50 per cent of the mean aortic pressure was obtained. This effect was attained with halothane concentrations that varied between 2 and 3 per cent in the inspired volume, after about 10 to 20 minutes of starting halothane administration. We performed 33 of these experiments in 17 dogs. In five of these dogs and in six others, we repeated the same maneuvers but we intended to prevent the aortic hypotension produced by halothane by controlled occlusion of the descending aorta with a snare.

In five of the dogs without aortic occlusion, the effect of halothane after beta-adrenergic blockade produced by the administration of propranolol (1 mg/kg, iv) was also studied. The blockade was assessed by the decrease to constant magnitudes of the cardiac and pressor responses to isoproterenol (0.125–0.25 µg/kg, iv).

NONWORKING HEART PREPARATION

In seven dogs anesthetized with thiopental a large cannula was placed into the root of the aorta through the left brachiocephalic trunk. This cannula was

TABLE 1. Percentage Changes (Mean ± SEM) in Aortic Pressure, Heart Rate, Coronary Blood Flow, Coronary Resistance, and Oxygen Consumption of the Left Ventricle Produced in Dogs by Halothane with and without Aortic Occlusion

	Halothane	Halothane and Aortic Occlusion	P†
Diastolic aortic pressure	-48 ± 1.5* (n = 33)	-14 ± 2.7* (n = 25)	<0.001
Heart rate	-13 ± 2.5* (n = 33)	-8 ± 1.9* (n = 25)	<0.001
Diastolic coronary blood flow	-23 ± 3.7* (n = 33)	-2 ± 4.2 (n = 25)	<0.001
Diastolic coronary resistance	-31 ± 3.5* (n = 33)	-12 ± 4† (n = 25)	<0.001
Left ventricular oxygen consumption	-32 ± 6.3* (n = 4)	-15 ± 9 (n = 9)	<0.001
Left ventricular arterio-venous oxygen content difference	+4 ± 4.4 (n = 4)	-18 ± 3.6* (n = 9)	<0.001

* P < 0.005 vs. 100 per cent oxygen.

† P < 0.01 vs. 100 per cent oxygen.

‡ Halothane vs. halothane plus aortic occlusion.

- = decrease; + = increase; n = number of experiments.

TABLE 2. Percentage Changes (Mean ± SEM) in Aortic Pressure, Coronary Blood Flow, and Coronary Resistance in Dogs Produced by Halothane with and without Beta-adrenergic Blockade

	With Blockade (n = 8)	Without Blockade (n = 33)	P*
Diastolic aortic pressure	-47 ± 4.7	-48 ± 1.5	>0.9
Diastolic coronary blood flow	-30 ± 4.5	-23 ± 3.7	>0.2
Diastolic coronary vascular resistance	-29 ± 5.6	-31 ± 3.5	>0.8

* With blockade vs. without blockade.

- = decrease.

connected to a perfusing system consisting of a digital perfusion pump, a disc oxygenator, and a heating coil, in series. The temperature of the perfusing blood at the tip of the aortic cannula was maintained with an ultrathermostat (Colora) at 37 C, as measured with a thermistor (Yellow Springs Instrument Co.). The perfusing system was primed with heparinized dog blood. The hematocrits ranged from 22 to 42 per cent, with an average of 37 per cent. The lower hematocrit values were in three of the dogs in which the blood was diluted with Tyrode's solution with 5 per cent polyvinylpyrrolidone (mw 70,000) added to preserve the osmolarity. A cannula with several lateral holes was placed into the right ventricular cavity through the superior vena cava and connected to the disc oxygenator. This cannula collected the coronary venous return to the right heart cavities after the total heart bypass was performed. The inferior vena cava, the azygos vein and the pulmonary artery were ligated, as well as the ascending aorta around the aortic cannula. Immediately afterwards, the perfusion pump was started and the perfusion pressure in the aortic cannula maintained between 68 and 128 mm Hg. The coronary venous return to the right ventricular cavity was considered to represent total coronary blood flow¹¹ and was measured directly from the outflow of the right ventricular cannula by timed collections. This flow ranged from 60 to 172 ml/min in different animals and did not vary by more than 10 per cent in any experiment. A cannula with lateral holes was implanted into the left ventricular cavity through the apex of the heart to obtain the drainage of coronary flow into this chamber plus possible leakage of blood from the aorta in case of aortic incompetence. In none of the dogs was the flow through this cannula more than 5 per cent of the input flow to the aorta. Therefore, coronary vascular resistance was computed as the ratio between the mean perfusion pressure and the coronary venous return to the right cavities of the heart.

In one of the nonworking heart preparations the heart was allowed to beat (intraventricular pressure zero); in two dogs the heart was arrested at

TABLE 3. Percentage Changes in Coronary Vascular Resistance Produced by Halothane in the Nonworking Canine Heart

	Procedure	Change in Mean Coronary Vascular Resistance
Dog 1	Beating	-38
	Beating	-47
Dog 2	Fibrillating	-18
	Fibrillating	-30
Dog 3	Fibrillating	-24
	Fibrillating	-49
	Fibrillating	-22
Dog 4	Fibrillating	-21
Dog 5	Fibrillating	+1
Dog 6	Arrested	-23
	Arrested	-6
Dog 7	Arrested	-22
	Arrested	-10
\bar{X}_D		-24
SE		± 4
P		<0.001

- = decrease; + = increase; \bar{X}_D = mean of the difference.

the time of starting the bypass, and in four dogs fibrillation occurred. When the preparation was ready, the disc oxygenator was ventilated with 100 per cent oxygen, and after perfusion pressure became stable, the halothane vaporizer was connected to the input of the perfusing system to give halothane concentrations between 2 and 3 per cent in the oxygenator. Changes in coronary perfusion pressure usually appeared within 10 minutes of starting halothane administration. In the four dogs with fibrillated hearts, the effect of halothane was additionally studied during beta-adrenergic blockade of the heart following injection of 40 mg propranolol into the system.

Results

WORKING HEART PREPARATION

Effects of Halothane without Preventing Aortic Hypotension

Aortic pressure, heart rate, coronary diastolic flow, coronary diastolic vascular resistance, and left ventricular oxygen consumption were compared during inhalation of 100 per cent oxygen and during a steady aortic hypotension induced by inhalation of halothane. Table 1 (second column) shows the changes. In 33 experiments performed in 17 dogs, mean decreases of 48 per cent in diastolic aortic pressure, 13 per cent in heart rate, 23 per cent in coronary blood flow, and 31 per cent in diastolic coronary resistance were observed ($P < 0.001$, t tests

for paired data). In four experiments in which the oxygen consumption of the left ventricle was measured, a decrease of 32 per cent occurred ($P < 0.005$). The arteriovenous oxygen content difference of the left ventricle increased by 4 per cent, but the change was not significant ($P > 0.4$).

Effects of Halothane and Partial Occlusion of the Aorta

Table 1 shows the effects of halothane in 25 experiments in 11 dogs in which the ascending aorta was partially occluded during halothane administration to maintain diastolic aortic pressure. We failed to restore this pressure completely, and a mean decrease of 14% was still observed; however, the aortic pressure during occlusion was significantly higher than that without occlusion ($P < 0.001$, t test for unpaired data). In this circumstance heart rate decreased by a mean value of 8 per cent, diastolic coronary flow did not change, but coronary resistance decreased by 12 per cent ($P < 0.001$, t test for unpaired data) than that observed without occlusion of the aorta. In nine experiments in which the oxygen consumption of the heart was measured, a nonsignificant decrease of 15 per cent was observed. The arteriovenous oxygen content difference of the left ventricle decreased significantly ($P < 0.005$, t test for paired data) by 18 per cent.

Effect of Halothane during Beta-adrenergic Blockade with Propranolol

In table 2, this effect is compared with that observed without blockade. In eight experiments performed in five dogs, halothane was administered until a decrease in aortic pressure similar to that produced in the experiments without blockade was obtained. The concentration of halothane in the inspired gas necessary for this purpose also varied between 2 and 3 per cent. During blockade the halothane-induced changes in coronary blood flow and resistance did not differ significantly from those observed without blockade ($P > 0.8$).

NONWORKING HEART PREPARATION

Table 3 shows the effect of halothane on mean coronary vascular resistance of the nonworking heart in 13 experiments performed in seven dogs. Since no difference was observed among the results obtained in beating, fibrillating, and arrested hearts, all results were combined. In all but one experiment, the equilibration of the perfusing blood with halothane plus oxygen induced a decrease in mean coronary vascular resistance compared with the control stage in which the perfusing blood was equilibrated with oxygen only. The mean decrease was

24 per cent and was significantly different from zero ($P < 0.001$, t test for paired data). In the four dogs with fibrillating hearts the effect of halothane after beta-adrenergic blockade with propranolol was also studied; in these experiments, halothane induced a mean decrease of 25 per cent in mean coronary vascular resistance. This decrease was not significantly different from the decrease observed before blockade in the same dogs ($P > 0.04$, t test for paired data).

Discussion

The results here reported show that halothane in a concentration of 2–3 per cent in inspired oxygen produces a decrease in the diastolic coronary resistance of the canine heart. This effect was observed in spite of a concomitant decrease in myocardial oxygen demand, a condition that tends to produce an increase in coronary resistance by metabolic autoregulation of the coronary vessels. Besides, the effect was observed in the isolated heart, a condition that eliminates the possibility that the decrease in resistance was mediated through extracardial neurohumoral factors. However, since halothane decreases the contractility and the afterload of the heart,^{2,4–8} the possibility that the decrease in resistance was due to a decrease in the extravascular component of the coronary resistance could be raised. This component is determined by: a) the magnitude of the intramyocardial pressure, which in turn is a function of the passive parietal stress in equilibrium with the intraventricular pressure; b) the strain imposed by myocardial shortening; c) myocardial contractility.¹² Our experimental conditions discard the effects of these factors because: a) In the working heart, coronary resistance was calculated during diastole, that is, when the intramyocardial pressure is minimal. The mechanical impediment to flow should be similar during the control state and during halothane administration unless a large increase in left ventricular diastolic pressure be produced by the drug, but in this case an increase in diastolic coronary resistance should be expected.¹³ b) The decrease in resistance was observed also in the fibrillating and the arrested hearts, conditions in which intramyocardial pressure, strain and contractility are nearly zero.¹² On the other hand, the fact that the decrease in resistance produced by halothane in the working heart was less than that observed in the nonworking heart (12 and 24 per cent, respectively) reveals that the decrease in resistance was partially masked by the mechanical impediment to flow produced by contraction of the heart.

Our results, then, suggest that the decrease in coronary resistance produced by halothane is the result of a direct vasodilatory action of the drug itself on the coronary vessels. These results agree with those obtained by Vatner and Smith in the con-

scious dog.⁴ According to these authors, the direct vasodilatory action of halothane on coronary vessels is counteracted by a tendency to vasoconstriction due to the decrease in the metabolic rate of the heart; when the anesthetic was administered in a relatively high concentration (2 per cent end-tidal), the direct vasodilatory action predominated. In their experiments, however, the possibility that the vasodilatation might result from myocardial ischemia could not be disregarded, since aortic pressure was not kept at control level and since the arteriovenous oxygen content difference of the heart was not measured.⁴

Our results also agree with those reported by Weaver *et al.*,¹⁴ who also studied the effect of halothane on coronary blood flow by measuring left circumflex flow with an electromagnetic flowmeter. Although these investigators comment that coronary flow decreased in the same proportion as blood pressure, in figure 4 of their report they show a significant ($P < 0.05$) decrease of coronary resistance to 70 per cent of the control value. Besides, this effect was accompanied by an increase in coronary-sinus blood oxygen saturation and a reduction of the arteriovenous oxygen content difference of the left ventricular wall.

Wolf *et al.*¹ reported that coronary blood flow decreases in proportion to the decrease in oxygen demand during halothane administration, and therefore no direct action of halothane on the coronary vasculature would occur. It is difficult to offer an explanation for the discrepancies between their results and ours, since in their experiments nitrous oxide and succinylcholine or thiopental were continuously administered. However, in the experiments on the nonworking beating heart performed by Wolf *et al.*, although the vascular component of coronary resistance increased during administration of halothane, the arteriovenous oxygen content difference for the heart did not remain close to control values, but instead greatly decreased; this suggests that the coronary vasoconstriction was not proportional to the decrease in oxygen consumption and that a vasodilatory action may have been present. The difference in net effects between their experiments (vasoconstriction) and ours (vasodilatation) may then reflect the greater concentration of halothane we used (2–3 per cent against 2 per cent) and the fact that since almost all our nonworking heart preparations were nonbeating, the reduction of myocardial metabolic demand and tendency to autoregulatory vasoconstriction should have been much less in our studies.

Our results differ from those of Smith *et al.*,³ who reported an increase of 15 per cent in coronary resistance, and from those of Merin *et al.*,² who found no change in resistance during halothane administration. Differences in the methodology used may account for the discrepancies;

thus, in these two studies the coronary resistance was computed using mean instead of diastolic flow values. Vasodilatation of small magnitude, as appears to have been the case in our working heart preparation (diastolic coronary resistance decrease of 12 per cent) may be easily overlooked when mean flow is used for calculation of coronary blood flow, since according to the waterfall theory of the coronary circulation,¹⁵ when intramyocardial pressure overcomes coronary outflow pressure during systole, the tonus of the coronary arterioles and precapillary sphincters is not a determining factor in vascular resistance. It is during diastole that this tonus becomes a regulating factor of resistance. The greater decrease in coronary resistance produced by halothane in the nonworking heart compared with the working heart developing nearly normal pressure, as here reported, support his view. Furthermore, in the experiments by Smith *et al.*,³ halothane was administered in concentrations in the inspired air that were lower than those used in ours (0.5–1.5 per cent *vs.* 2–3 per cent). At a concentration of 1 per cent Smith *et al.* observed a 30 per cent decrease in myocardial oxygen consumption and a 15 per cent increase in coronary resistance; when the halothane concentration was increased to 1.5 per cent, myocardial oxygen consumption decreased further to 54 per cent, but coronary resistance did not increase further as would be expected. This result suggests that the coronary vasoconstriction that normally follows a decrease in cardiac oxygen demand was counteracted by halothane. This interpretation agrees with the results of Vatnes and Smith⁴ and ours.

It has been suggested^{16,17} that halothane activates beta-adrenergic receptors. Our results, however, show that the vasodilatory effect of halothane on the coronary circulation is not mediated through this activation, since the decreases in coronary resistance were of the same magnitude before and during beta-adrenergic blockade with propranolol. This finding is similar to those reported for other vascular beds such as the renal, iliac and mesenteric.⁴

In conclusion, our results in the working and in the nonworking isolated heart suggest that halothane has a direct vasodilatory effect on the coronary circulation.

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