

The Effect of Halothane on Reflexes Elicited by Acute Coronary Artery Occlusion in the Dog

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Acute myocardial infarction in the intra- or perioperative period may be accompanied by either bradycardia and hypotension or tachycardia and hypertension. Different degrees of activation of cardiac and arterial receptors stimulated by the infarction may produce the seemingly dichotomous results. When infarction occurs intraoperatively, the effects of anesthesia may also play a role on the reflex responses observed. This study was performed for two reasons: 1) to study the effects of acute coronary artery occlusion (ACO) on vascular resistance; and 2) to study the effects of halothane (H) anesthesia on this ACO reflex. Snare occlusions of the left coronary arteries were performed in pentothal-anesthetized mongrel dogs, and changes in arterial pressure, left ventricular length, hindlimb vascular resistance, and lumbar sympathetic efferent nerve activity were measured during 30- to 60-s occlusions at 0, 0.5, 1.0, and 1.5 per cent end tidal halothane concentrations.

ACO produced a consistent depressor response, produced by withdrawal of sympathetic efferent activity, that was significantly attenuated by vagotomy. Increasing levels of H blunted the reflex depression in vascular resistance, and also produced decreases in baseline resistance and increases in left ventricular end diastolic length (LVEDL). Vagotomy blunted the dose-dependent decrease in baseline resistance with H. Therefore, the study has shown that: 1) ACO activates vagal afferents to initiate a reflex decrease in vascular resistance; 2) this reflex dilation is attenuated with increasing levels of H; and 3) by producing increases in LVEDL, H stimulates cardiac receptors and reflexly reduces vascular resistance. (Key words: Anesthetics, volatile: halothane. Blood pressure: peripheral vascular resistance. Heart: coronary occlusion; cardiovascular reflexes. Sympathetic nervous system: reflexes.)

ACUTE MYOCARDIAL INFARCTION in the intra- or perioperative period may produce serious hemodynamic consequences or may remain relatively unnoticed except for later changes in the ECG and serum concentrations of myocardial enzymes. Acute coronary occlusion in animal models has been shown to produce

either a pressor or a depressor response initiated by receptors located in the myocardium and distributed throughout the left and right ventricles.¹ The depressor changes associated with decreases in vascular resistance due to acute coronary occlusion may occur in sinoaortic baroreceptor denervated animals.¹ This depressor reflex may also be reproduced by electrical stimulation of pericoronary afferent vagal fibers.² Impairment of reflex vasoconstriction has been observed clinically in patients with acute myocardial infarction.³ In one study, 45 per cent of the patients seen within 30 min after onset of an infarction exhibited bradyarrhythmia and hypotension, while only 33 per cent showed evidence of tachycardia and hypertension.⁴ These different responses to the infarct may be the result of varying degrees of afferent input from cardiopulmonary receptors and arterial baroreceptors in each individual. The present study explores the role of cardiopulmonary reflexes in the clinical expression of intra- or perioperative myocardial infarction. Our objectives were twofold: 1) to study the effects of acute left circumflex or left anterior descending coronary artery occlusion on vascular resistance in a muscular (isolated gracilis muscle) and muscular-cutaneous (isolated hindlimb) vascular bed; and 2) to study the effects of halothane anesthesia on this acute coronary occlusion reflex.

Methods

Twenty mongrel dogs (18–25 kg) were anesthetized with two types of basal anesthesia in three experimental protocols. The carotid sinus nerves, sympathetic ansae subclavia, and parasympathetic vagus nerves were bilaterally located and marked with loose ligatures for later section. Group I consisted of five animals in which changes in hindlimb vascular resistance were recorded during acute coronary occlusion. Group II consisted of five animals in which changes in vascular resistance in the isolated gracilis muscle were recorded during acute coronary occlusion. Both Group I and Group II animals were lightly anesthetized with thiopental, 20–25 mg/kg, iv, paralyzed with pancuronium, 0.1 mg/kg, intubated and ventilated with 50 per cent N₂O–O₂ and 0.5 per cent halothane prior to 30- to 60-s coronary artery occlusions. Following control occlusions, the carotid sinus nerves, the ansae subclavia, or vagus nerves were

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randomly sectioned, and the occlusions repeated. The time required for surgery before occlusion (1.5–2 h) provided a period for metabolic degradation or redistribution of thiopental, which reduced its effect on the reflex studied. Each of the remaining nerves were then randomly cut and the occlusion again repeated. Thirty min were allowed between nerve sections to permit conditions to stabilize.

Group III consisted of ten animals in which changes in hindlimb vascular resistance during both coronary occlusion and varying halothane concentrations were recorded. Group III animals were anesthetized with thiopental, 20–25 mg/kg, paralyzed with pancuronium, 0.1 mg/kg, intubated and ventilated with 50 per cent N₂O–O₂. Atropine (0.4 mg/kg) and propranolol (1 mg/kg) were administered to block cardiac responses to changes in efferent nerve activity, and to exclude the involvement of all known sympathetic and parasympathetic vasodilator mechanisms, with the exception of withdrawal of central sympathetic vasomotor tone. Atropine and propranolol had no direct effect on blood pressure. Halothane was increased from 0 per cent to 0.5 per cent, 1.0 per cent, and 1.5 per cent in a stepwise fashion with 20-min equilibration between concentration changes. Coronary occlusions (30–60 s) were performed at each level. Thirty min following discontinuation of halothane and bilateral cervical vagotomy, the stepwise increase in halothane was repeated.

In all animals, anesthetic gases were administered by means of a Foregger anesthesia machine. Halothane was given via a Fluotec[®] Mark II vaporizer and monitored with a Beckman[®] end-tidal halothane analyzer. Moderate hyperventilation (Pa_{CO₂} 25–35 torr) was achieved with a Bird[®] Mark 7 respirator and Mark 4 anesthesia assistant/controller. Pa_{O₂} was greater than 90 torr. A femoral artery was cannulated for direct blood pressure measurement via a Statham[®] pressure transducer. A femoral venous line was used for drug administration. The brachial arteries were cannulated and connected to a three-liter pressurized reservoir primed with one liter of heparinized Dextran[®] 75. By adjusting air inflow and outflow, this device provided isobaric control of blood pressure.⁵ Via a midline sternotomy, loose snares were placed around the left circumflex and left anterior descending coronary arteries. Only the data obtained from left circumflex artery occlusions were used in the present study, for these occlusions were found to stimulate a greater portion of the left ventricle. A Whitney length gauge was sutured to the epicardium of the left ventricle in the region supplied by the circumflex artery. Carotid sinuses were either isolated for later denervation or, in Group

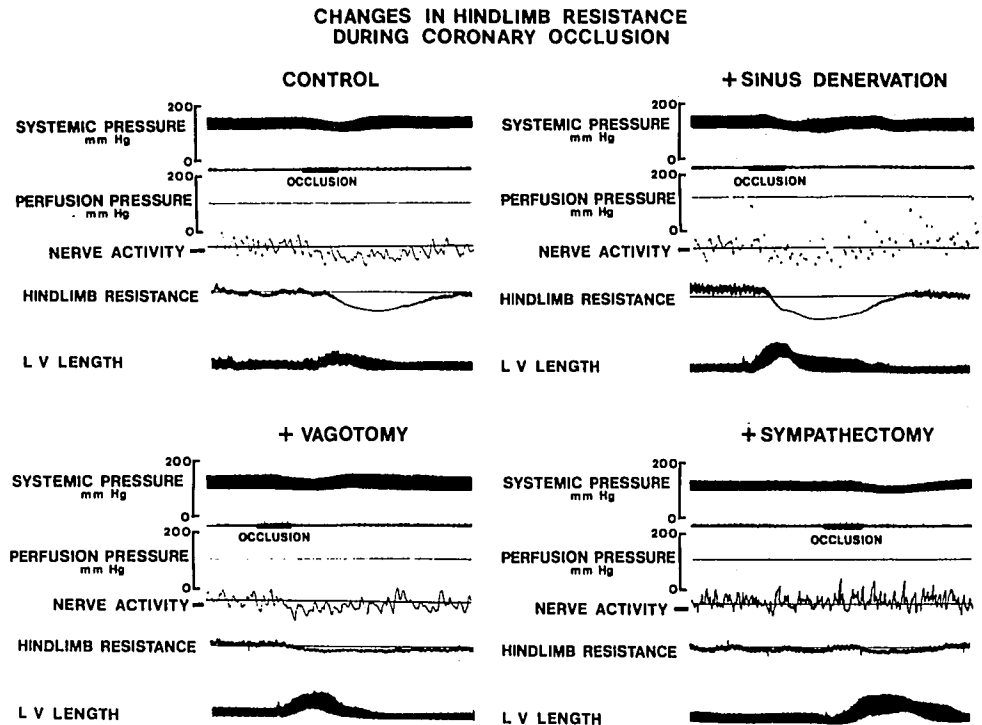
II, perfused at constant pressure using the servo-control techniques described below. For perfusion of the isolated hindlimb, the femoral artery was isolated and all other collaterals to the limb ligated. With blood obtained from the cannulated proximal femoral artery, the distal femoral artery was then cannulated and perfused with halothane-containing blood with a Sarns roller pump at constant pressure using a servo-control system. The servocontrol unit increased or decreased pump speed in response to an error signal between desired and actual perfusion pressures measured at the tip of the cannula via a Statham[®] pressure transducer. The response time of the servocontrol unit (1 s) allowed only brief alterations in perfusion pressure. It provided an on-line reading of electrically-derived relative units of resistance and flow. Perfusion pressure, flow, and resistance of the hindlimb were recorded on a Grass model 7 recorder. The isolated gracilis muscle preparation utilized a Holter pump delivering 8–12 ml/min at constant flow, with changes in perfusion pressure indicating changes in vascular resistance. The Holter pump could not be used to produce constant pressure perfusion. The gracilis muscle was isolated, with all arteries except the gracilis artery ligated. Nerve supply to the muscle is primarily associated with the gracilis artery and was therefore not damaged. The gracilis artery was then carefully isolated and cannulated and perfused with blood drawn from the femoral artery. The post-ganglionic efferent lumbar sympathetic nerve activity was recorded in five animals of Group III. A branch of the lumbar sympathetic chain which extended to the hindlimb was isolated and sectioned, and the central end was drawn into a nerve tank and covered with warm mineral oil. The nerve was desheathed and placed on tungsten carbide chloride electrodes connected to a high-gain preamplifier, amplifier system which was directed to a Tandberg FM tape recorder. Nerve activity was also electrically averaged and recorded on the Grass polygraph. Systemic blood pressure, lead II ECG, LV length, and end-tidal halothane concentrations were recorded. Data were analyzed by Student's unpaired *t* test in Group I and II, and with the paired *t* test in Group III.

Results

GROUP I

In the isolated hindlimb preparations, acute coronary occlusion produced a consistent depressor response in hindlimb vascular resistance that was markedly attenuated by bilateral vagotomy ($P < 0.025$), with the small residual change totally eliminated by thoracic sympathectomy (fig. 1). There

FIG. 1. Reflex changes in lumbar sympathetic efferent nerve activity and hindlimb resistance during acute coronary artery occlusions. Note that changes in each do not occur until dilation of the ischemic left ventricular segment occurs. Most of the reflex changes are eliminated by vagotomy, but are actually enhanced by elimination of the buffering carotid sinus baroreceptors.



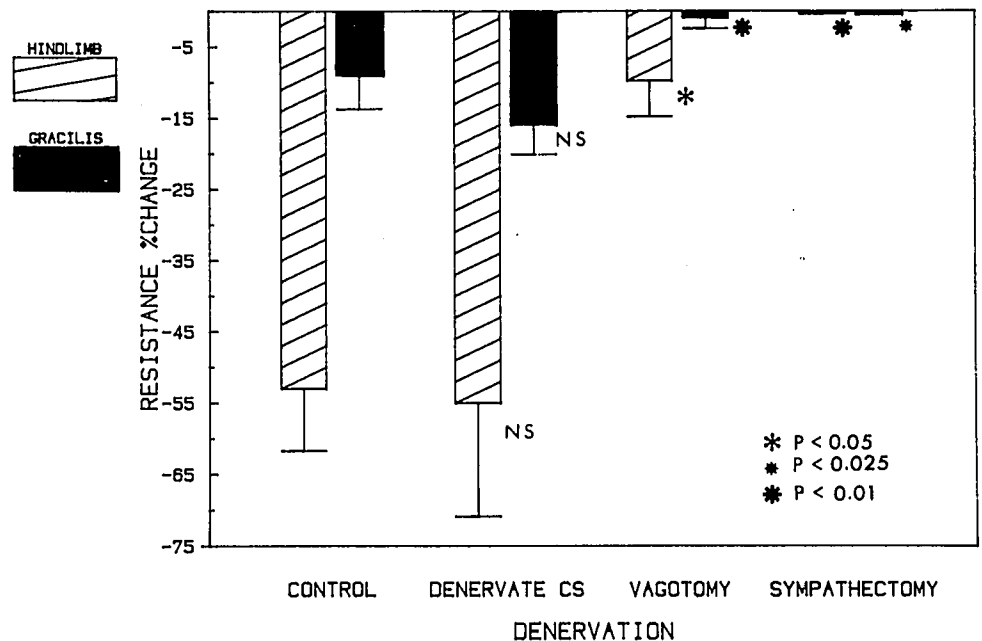
was no significant difference in the depression in vascular resistance between five dogs on the isobaric system with intact carotid sinus innervation (mean = 2.67 resistance units) and three dogs subsequently denervated (mean = 3.29 resistance units; fig. 2).

GROUP II

In the constant-flow perfused gracilis muscle, acute coronary occlusion produced a consistent depression

in vascular resistance indicated by a fall in perfusion pressure (fig. 2). In five dogs with intact carotid sinus baroreceptor nerves, the decrease in gracilis muscle perfusion pressure averaged 13 torr. During constant pressure carotid sinus perfusion, the average decrease in gracilis muscle perfusion pressure produced by acute coronary occlusion was 21.4 torr. These differences were not statistically significant. Bilateral vagotomy eliminated the depressor reflex

FIG. 2. Reflex resistance responses in the isolated hindlimb and gracilis muscle to acute coronary artery occlusion. While carotid sinus denervation did not significantly change the reflex dilation produced by occlusion, vagotomy significantly attenuated the response in both beds. Thoracic sympathectomy eliminated any measured response. Each reflex change is compared to the change that directly precedes it. (n = 5 for each bed, mean ± SE).



EFFECT OF HALOTHANE ON THE CORONARY OCCLUSION REFLEX

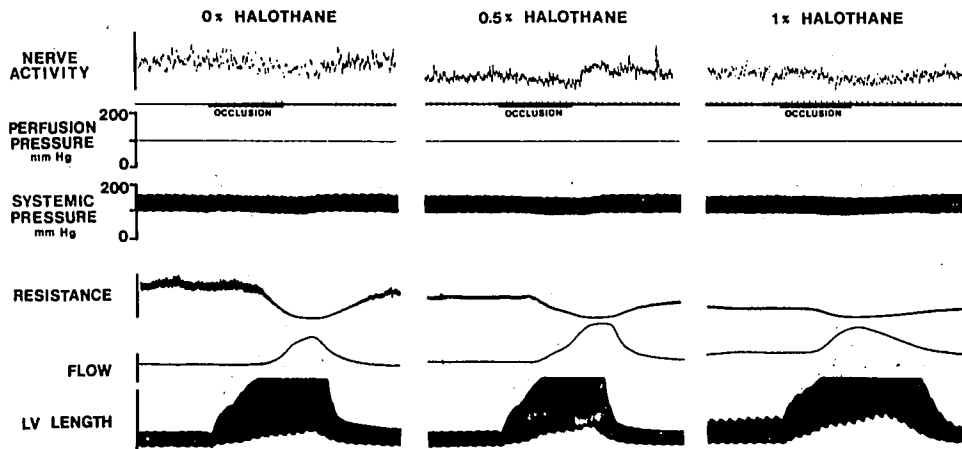


FIG. 3. The effects of halothane on the reflex resistance changes in the isolated hindlimb during coronary occlusion. Increasing levels of halothane blunted the reflex dilation occurring with occlusion. This attenuation was accompanied by decreases in sympathetic efferent nerve activity and baseline hindlimb resistance and increases in hindlimb flow and left ventricular end-diastolic length.

($P < 0.025$), but sympathectomy failed to have an effect.

In both Groups I and II, the depression in vascular resistance during acute coronary occlusion paralleled the increase in left ventricular segmental length produced by ischemic myocardial dilatation (fig. 1).

GROUP III

The effect of halothane on the coronary artery occlusion reflex is shown in figure 3 and table 1. Increasing concentrations of halothane blunted the reflex depression of hindlimb vascular resistance due to acute coronary artery occlusion. As seen in figure 4, without exposure to halothane the mean depression in vascular resistance with acute coronary occlusion was 4.9 resistance units (RU); with 0.5 per cent halothane 2.2 RU, a significant difference ($P < 0.05$). One per cent and 1.5 per cent halothane significantly depressed the reflex changes in vascular resistance with coronary occlusion further from control, but the changes between 0.5, 1.0, and 1.5 per cent halothane concentrations were not significantly from each other.

Concomitantly, halothane produced a dose-related depression in baseline hindlimb vascular resistance

(fig. 3, table 1). Prior to vagotomy, the introduction of 0.5 per cent halothane dropped mean resistance significantly from 14.9 RU to 6.74 RU ($P < 0.01$) (fig 5). Increasing halothane to 1.0 per cent caused a further significant decline to 4.42 RU ($P < 0.05$). Vagotomy alone did not alter baseline hindlimb resistance in the absence of halothane. (mean = 14.9 RU pre-vagotomy *vs.* mean = 14.82 RU postvagotomy). As indicated in figure 5, and table 1, vagotomy altered the effect of halothane on baseline hindlimb vascular resistance. In animals serving as their own control at 0.5, 1.0, and 1.5 per cent halothane, vagotomy significantly reduced the depression in baseline vascular resistance caused by halothane.

The effect of halothane was also apparent on left ventricular end diastolic length (LVEDL). Although 1 per cent halothane was required to produce a significant increase in LVEDL, the increase in segmental length tended to be dose related (fig. 3). Vagotomy had no significant effect on LVEDL.

Lumbar sympathetic postganglionic nerve activity decreased with the onset of ventricular dilation caused by acute coronary occlusion (fig. 1). It returned to baseline with the recovery of LVEDL. Halothane

TABLE 1. Effect of Halothane on Hindlimb Resistance in Resistance Units (RU)*

Halothane Concentration (Per Cent)	Initial Baseline Resistance Level	Reflex Resistance Level during Coronary Occlusion	Baseline Resistance Level	
			Prevagotomy	Postvagotomy
0.0	13.19 ± 2.18	8.30 ± 2.15	14.89 ± 2.54	14.82 ± 2.79
0.5	7.13 ± 0.64†	4.89 ± 0.80	6.74 ± 0.83	9.84 ± 1.53‡
1.0	5.52 ± 0.83†	3.66 ± 0.77	4.42 ± 1.01	7.04 ± 1.40‡
1.5	3.76 ± 0.84†	2.96 ± 0.30	3.58 ± 0.66	6.10 ± 0.79‡

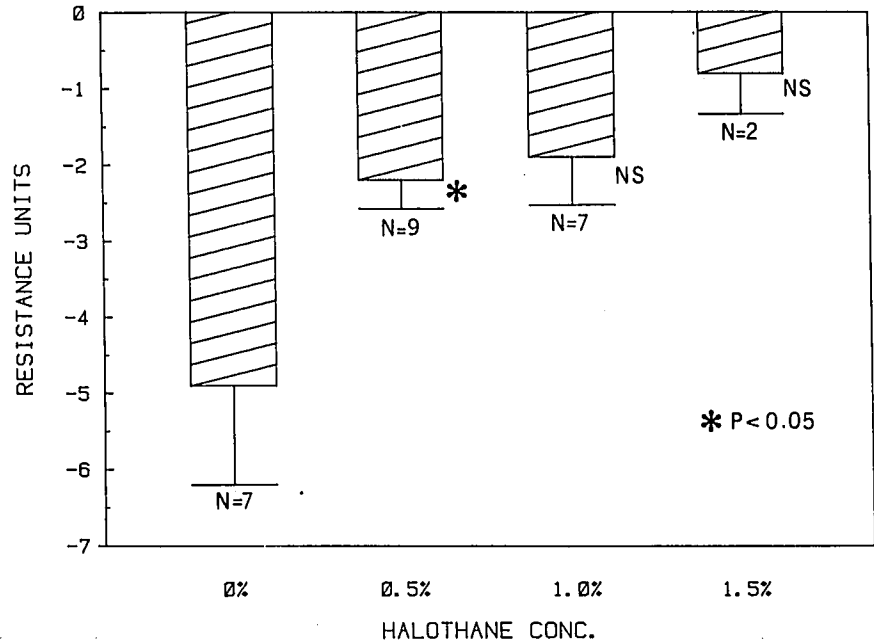
Values are means ± SE.

* Resistance units indicate torr/flow (rpm).

† Significantly different from 0.0 per cent, $P < 0.05$.

‡ Significantly different from prevagotomy levels at the same halothane concentration, $P < 0.05$.

FIG. 4. The effect of halothane on reflex changes in hindlimb resistance during coronary occlusion. Low levels of halothane (0.5 per cent) significantly reduced the reflex magnitude of the change in resistance (4.9 units to 2.2 units). Increasing halothane to higher levels further attenuated the response, but not to responses significantly different from those obtained at 0.5 per cent halothane (n = indicated for each group, mean \pm SE).



depressed sympathetic nerve activity in concentrations as low as 0.5 per cent, while subsequent changes in response to increasing concentrations were less apparent (fig. 3). Vagotomy produced a transient increase in sympathetic efferent nerve activity that gradually returned to baseline within 30 min.

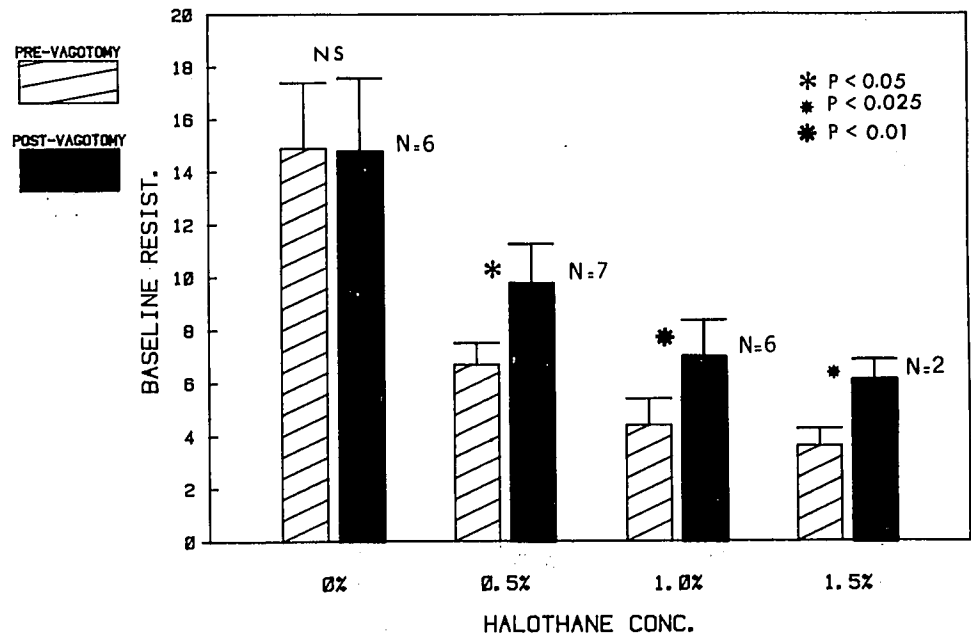
Discussion

In the present study, acute coronary artery occlusion produced regional myocardial ischemia, leading to myocardial dilation and the activation of left

ventricular (LV) mechanoreceptors. The activation of LV mechanoreceptors, which corresponded to measured increases in LV segmental length, initiated a vagal afferent reflex suppression of sympathetic outflow to the hindlimb and a decrease in peripheral vascular resistance.

The study has indicated that acute experimental coronary occlusion may initiate a number of different reflexes. If sufficient blood supply to the left ventricle is interrupted to produce a defect in global ventricular function, the resulting decrease in cardiac output and arterial blood pressure results in decreased stimu-

FIG. 5. The effects of halothane and vagotomy on baseline resistance levels in the isolated hindlimb. Halothane produced a dose-related decrease in hindlimb resistance both before and after vagotomy, but the decreases post-vagotomy were significantly less than those prevagotomy at all levels of halothane. Vagotomy, therefore, eliminated a portion of the decrease in hindlimb resistance induced by halothane. Note that pre- and postvagotomy control resistance levels (0 per cent halothane) were not significantly different from each other. (Mean \pm SE, n = indicated for each group).



lation of sinoaortic baroreflexes. If the coronary occlusion results in segmental left ventricular dysfunction without much change in cardiac output, either a depressor,^{6,7} or pressor^{8,9} response may occur in experimental animals and in humans.³ The present study found that elimination of the buffering influences of the carotid sinus baroreceptors enhanced the depressor response to occlusion which was mediated by left ventricular mechanoreceptors with vagal afferent pathways.² Earlier studies found that activation of cardiac receptors by coronary embolization produced vasoconstriction in a muscular bed and vasodilation in a cutaneous bed.^{9,10} This differential response was obtained in animals where the arterial baroreceptors were free to respond to any pressure changes. In the present study, with carotid sinus input controlled, both the isolated hindlimb and gracilis muscle showed vasodilation responses. Therefore, the reflex response of a combined cutaneous-muscular bed (hindlimb) did not differ from that of only a muscular bed.

The depressor reflex, when activated by acute segmental ventricular distention secondary to coronary occlusion, resulted in a vagally-mediated bradycardia and a decrease in hindlimb and muscular vascular resistance secondary to withdrawal of sympathetic efferent nerve activity. In the present study, a role for active vasodilation through either activation of beta-adrenergic or muscarinic-cholinergic mechanisms was eliminated since the responses were not altered after administration of propranolol and atropine.

The cardiopulmonary depressor reflex initiated by acute segmental coronary artery occlusion was altered by halothane in the present study. Halothane anesthesia blunted the magnitude of the depressor reflex to acute coronary artery occlusion. This occurred even at low levels of halothane (0.5 per cent) in conjunction with a depression in baseline sympathetic nerve activity and hindlimb resistance. The apparent decrease in reflex response may therefore be due to a direct depressant effect of halothane, to the fact that occlusion occurred when resistance was already depressed, or to both.

Halothane has multiple sites of action on the peripheral circulation. It depresses the central vasomotor centers and attenuates baroreflexes,¹¹ with an end-tidal concentration of 0.7 per cent producing a depression of baroreflex control of heart rate in humans.¹² Halothane also depresses sympathetic ganglionic transmission^{13,14} and has a direct depressant effect on vascular smooth muscle¹⁴ and myocardial contractile force.¹⁵ Finally, halothane has been shown to increase left ventricular end diastolic pressure and volume in

humans,¹⁶ and was found to increase left ventricular end diastolic length in the dog in the present study.

The nature of halothane's interaction with cardiopulmonary reflexes is as complex as its hemodynamic effects. Depression of vasomotor centers, ganglionic blockade, direct vascular and cardiac depression, and depression of carotid sinus buffering influences may all contribute to the alteration of cardiopulmonary reflexes including the coronary artery occlusion reflex.

It appears that reflex hindlimb vasodilation in the present study was influenced by halothane in at least two different ways. The increase in left ventricular circumference and segmental length associated with halothane stimulated left ventricular mechanoreceptors to suppress central sympathetic efferent activity and thereby decrease peripheral vascular resistance. Interruption of vagally-mediated cardiopulmonary afferent activity from these receptors by means of bilateral vagotomy decreased the degree of peripheral vascular depression accompanying increasing levels of halothane. This blunting of halothane-induced dilation occurred in the absence of changes in control (0 per cent halothane) resistance following vagotomy. In addition a direct effect of halothane unmasked by vagotomy on either the central centers, the peripheral vasculature, or both produced a decrease in baseline vascular resistance and sympathetic efferent nerve activity associated with increasing blood levels of halothane. These effects may have contributed to the overall decrease in reflex vasodilation during halothane anesthesia.

These studies indicate that not only the detection of acute coronary occlusion may be more difficult during general anesthesia with halothane, but also the reflex response of the cardiovascular system to acute coronary occlusion may be modified by halothane anesthesia. Altered clinical responses to acute coronary artery occlusion during anesthesia may be the result not only of halothane's direct depression of central and peripheral vasomotor mechanisms, but may also be due to activation of cardiopulmonary vagal reflexes caused by changes in central blood volume and cardiac chamber size.

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