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Intestinal Circulation during Inhalation Anesthesia

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This study was designed to evaluate the influence of inhalational agents on the intestinal circulation in an isolated loop preparation. Sixty dogs were studied, using three intestinal segments from each dog. Selected intestinal segments were pumped with aortic blood at a constant pressure of 100 mmHg. A mixture of ^{86}Rb and 9-μm spheres labeled with ^{141}Ce was injected into the arterial cannula supplying the intestinal loop, while mesenteric venous blood was collected for activity counting. A very strong and significant correlation was found between rubidium clearance and microsphere entrapment ($r = 0.97$, $P < 0.0001$), suggesting that the shunting of 9-μm spheres through the intestines reflects the arteriovenous shunting of blood. Nitrous oxide anesthesia was accompanied by a higher vascular resistance (VR), lower flow (F), rubidium clearance (Cl-Rb), and microspheres entrapment (Cl-Sph) than pentobarbital anesthesia, indicating that the vascular bed in the intestinal segment was constricted and flow (total and nutritive) decreased. Halothane, enflurane, and isoflurane anesthesia were accompanied by a much lower arteriovenous oxygen content difference ($AVDO_2$) and oxygen uptake than pentobarbital or nitrous oxide. Compared with pentobarbital, enflurane anesthesia was not accompanied by marked differences in VR, F, Cl-Rb, and Cl-Sph; halothane at 2 MAC decreased VR and increased F and Cl-Rb while isoflurane increased VR and decreased F. α-Adrenoceptor blockade with phentolamine (1 $mg \cdot kg^{-1}$) abolished isoflurane-induced vasoconstriction, suggesting that the increase in VR was mediated via circulating catecholamines. Decreases in mesenteric blood flow, which always have been observed during inhalation anesthesia, primarily are caused by the indirect effects of anesthetics mediated through changes in systemic circulation and the central nervous system. Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: enflurane; halothane; isoflurane. Gastrointestinal tract: intestines, blood flow, metabolism. Measurement techniques: blood flow, microspheres.

THE CIRCULATORY RESPONSE to inhalation anesthesia has been studied extensively and involves a decrease in blood pressure and cardiac output.[1] Regional blood flow is regulated by many factors (local, nervous, and humoral) influencing the circulation directly and indirectly.[2] Changes in regional blood flow during inhalation anesthesia can be mediated through central mechanisms, which may depend on a reduction in cardiac output and changes in vascular tone, due to changes in various humoral substances such as epinephrine, histamine, serotonin, and many others, Finally, these alterations may be induced by a direct influence of an anesthetic on one or another area of the peripheral circulation. The splanchnic circulation may play an important role in alterations and maintenance of homeostasis during anesthesia.[3] It has been shown that all inhalational anesthetics decrease blood flow through the gut.[4–11] A reduction in splanchnic blood flow is associated with a decrease in cardiac output.[5,12,13] Therefore, it is not clear as to what extent the observed decrease in splanchnic blood flow depends on a decrease in cardiac output (and/or a reduction in blood pressure), a decrease in metabolism and oxygen requirements with a subsequent decrease in blood flow, or a direct influence of anesthetics on the regional circulation. This study was designed to evaluate the influence of inhalational anesthetics on the intestinal circulation in an isolated loop preparation, allowing determination of the direct and hormonal effects of anesthetics on the peripheral circulation. Another objective of the present study was to compare the clearance of rubidium with the entrapment of 9-μm spheres during inhalation anesthesia in order to verify whether entrapment of 9-μm spheres still would reflect nutritive blood flow under the effects of inhalational anesthetics as it did under different pathophysiologic conditions during pentobarbital anesthesia.[14]

Methods

Experiments were performed on 60 mongrel dogs of either sex, weighing 15–20 kg. Thirty-one dogs (control group) were anesthetized with intravenous pentobarbital sodium 30 $mg \cdot kg^{-1}$ initially and supplemented as required. The remaining 29 animals (experimental groups) were anesthetized with methohexital sodium, 4 $mg \cdot kg^{-1}$. Muscle relaxation was achieved with pancuronium, 0.1 $mg \cdot kg^{-1}$. Controlled ventilation, adjusted to maintain arterial CO_2 tension at 35–40 mmHg, was provided with an Air Shield® ventilator through an endotracheal tube in all of the animals. Femoral arteries and veins were exposed and cannulated; 100 ml of blood was collected and replaced with 350 ml of Ringer's lactated solution. This blood was used during the experiment to replace blood taken for analyses. Ringer's lactated solution was infused through the left femoral vein at a constant rate of 15 $ml \cdot kg^{-1} \cdot h^{-1}$.

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A laparotomy was performed and a segment of the small intestine, supplied by a vascular arcade arising from a single mesenteric artery and vein, was selected. The method of the isolated loop preparation has been described previously.[14] Short segments of the mesenteric artery and vein were dissected free of the mesentery. Heparin, 5 $mg \cdot kg^{-1}$ iv, was administered. The mesenteric vein was transsected and cannulated with polyethylene tubing of appropriate size. Blood from the mesenteric vein was collected in a reservoir placed at the level of the mesenteric vein to achieve a mesenteric venous pressure of 0 mmHg. This blood was pumped back into the dog through a femoral vein. When the venous drainage was established, the artery was transsected and cannulated, and arterial blood was pumped from the aorta through the chosen intestinal segment (using a Holter precision roller pump) at a constant pressure of 100 mmHg. The isolated loop with cannulated vessels was completely separated from the animals' body and placed between saline-soaked gauzes and plastic wrap and temperature maintained at 37–38° C with an electrical pad.

Aortic pressure (via a femoral artery cannula) and perfusion pressure (pressure in arterial limb between pump and the intestinal segment) were recorded with Statham® transducers and a Grass® polygraph.

After 30 min of stable perfusion and mean arterial pressures, arterial and mesenteric venous blood samples were taken for *p*H and oxygen content determinations. A mixture of ^{86}Rb and 9-μm spheres labeled with ^{141}Ce was injected within 15 s into the arterial cannula supplying the intestinal loop (the port of injection was placed between the femoral artery and the pump), while mesenteric venous blood was collected in test tubes for 3 min (15 s for each test tube) for activity counting. The collection of mesenteric venous blood was begun 10 s prior to the injection of the rubidium and microspheres. After 3 min of blood collection, pump perfusion was terminated and the intestinal segment was divided into four to six pieces and processed for activity counting. Blood drained from the mesenteric vein was replaced with blood that had been collected at the beginning of the experiment. Then, another intestinal segment was prepared and processed the same way. Three intestinal segments were used from each dog.

Ten to 15 min were required for the preparation of each isolated intestinal segment. An additional 10 to 15 min were needed to stabilize perfusion pressure. This period was followed by 30 min of stable perfusion and mean arterial pressures, and then another 5 min were required for blood sampling and rubidium and microspheres injection. Thus, each stage of the experiment lasted about 1 h, and the measurements of circulatory variables were performed at the end of the hour, which provided sufficient time for tissue saturation with an anesthetic.

The first intestinal segment was studied under nitrous oxide anesthesia (66% N_2O) in the 29 dogs. The second and third loops were studied under isoflurane, enflurane, and halothane anesthesia (eight dogs per group), where 1 or 2 MAC of anesthetic was used in random order and 0.9 end-expired halothane, 2.2% end-expired enflurane, and 1.5% end-expired isoflurane were considered to equal 1 MAC. In the remaining five dogs, similar experiments were performed under isoflurane anesthesia (2 MAC) and α-adrenocepter blockade. Phentolamine, 1 $mg \cdot kg^{-1}$, was injected intravenously and isoflurane, 3–5% inspired, provided for 5 to 7 min to achieve the desired concentration of 3% end-expired. The measurements were performed at 9–12 min after phentolamine injection when inspired/expired isoflurane concentration ratio approached 0.6. End-expired concentration of isoflurane at the time of measurements was stable for 5 min at 2 MAC, and the flow through the loop was adjusted to achieve perfusion pressure at 100 mmHg.

Inhalational anesthetics were administered through a Foregger® Copper Kettle with a North American Drager anesthesia machine. End-expired concentrations of inhalational anesthetics were measured constantly with an Engström® Multigas Monitor for Anesthesia (EMMA). With a 30-min warm-up period, the EMMA was zeroed against room air. A humidity retaining device, "artificial nose," separated the EMMA sensor from the animals' humidified air. In this case, water vapor values consistently showed 0.5%; therefore, the actual value of end-expired isoflurane concentration was equaled to a read-off value minus 0.5%. The EMMA was calibrated with a calibration transducer provided by the Engström Company. Thirty random EMMA measurements were compared with measurements obtained with the Perkin-Elmer® Medical Gas Analyzer, Model 1100, and the values were found to be identical.

Oxygen tension and *p*H were measured with an Instrumentation Laboratories model 813 *p*H/blood gas analyzer. Oxygen content was measured with an Instrumentation Laboratories CO-oximeter 282.® Each shipment of microspheres (purchased from 3M Co.) was checked for size of spheres (determined with a standard Coulter Counter® routinely used for determination of red blood cell size), fragmentation, and status of aggregation.[15] Microspheres were used only when size variations did not exceed standard deviations of 1 μm. Microspheres were labeled with ^{141}Ce and suspended in a 10% dextran solution with polysorbate (Tween 80). Microspheres were mixed in a special injector[15] with ^{86}Rb and diluted in 3 ml of normal saline. Each injection contained about 10^6 of spheres and approximately 300

μCi of rubidium. Each of the isotopes generated approximately 0.5×10^6 counts/min.

Radioactivity in the intestinal segment and mesenteric venous blood samples was analyzed with a Tracor 2250® gamma counting system (Tracor Northern). This system utilizes the least-squares "fitting" technique to resolve the amount of radioactivity contributed by each isotope (^{141}Ce and ^{86}Rb in this case) in gamma ray spectra obtained by an NaI detector for the individual tissue and blood samples.[14,16,17] The method employs an isotope calibration file that contains the decay rate, the number of counts per microspheres, and the spectral definition of each isotope used in the study. Once loaded into memory, this calibration file was used by the Microsphere Analysis Program to conduct a comparison of the spectra contained in the file (standard spectra) and the spectra of the blood or tissue sample.

Total blood flow for each intestinal segment was measured directly by the amount of blood drained from the mesenteric vein. Each segment was weighed after the experiment and blood flow (F), calculated in $ml \cdot min^{-1} \cdot g^{-1}$. Vascular resistance (VR) was calculated as follows:

$$VR\ (dyn \cdot s \cdot cm^{-5} \cdot g) = \frac{\text{Perfusion pressure (mmHg)}}{\text{blood flow } (ml \cdot min^{-1} \cdot g^{-1})} \times 1{,}333$$

Arteriovenous oxygen content difference was calculated and expressed in ml/dl of blood. Oxygen uptake was calculated by multiplying intestinal blood flow by arteriovenous oxygen content difference. Rubidium and 9-μm sphere clearances were calculated as follows: Cl-Rb = F × (Rb injected − Rb venous)/Rb injected, and Cl-Sph = F × (Sph injected − Sph venous)/Sph injected, where F is intestinal blood flow in $ml \cdot min^{-1} \cdot g^{-1}$; Rb injected and Rb venous are rudidium activity injected into and recovered from the intestinal segment, respectively, and Sph injected and Sph venous are numbers of 9-μm spheres injected into and recovered from the intestinal segment, respectively.[14] The activity injected into the segment was compared with activity found in the blood and intestinal segment.

Data were summarized as the mean ± standard error of the mean. Differences between groups and control values (pentobarbital or nitrous oxide) were tested by the use of a one-way analysis of variance. Differences between levels of the same drug were tested by use of a randomized block analysis. Individual comparisons between pairs of means were performed using Fisher's protected least significant difference test.[18] Pearson's correlation coefficient and the corresponding least-squares regression equation were used as the measure of association when comparing two response measurements. Differences were considered significant if $P < 0.05$. All computations were performed with the aid of the Statistical Analysis System.[19]

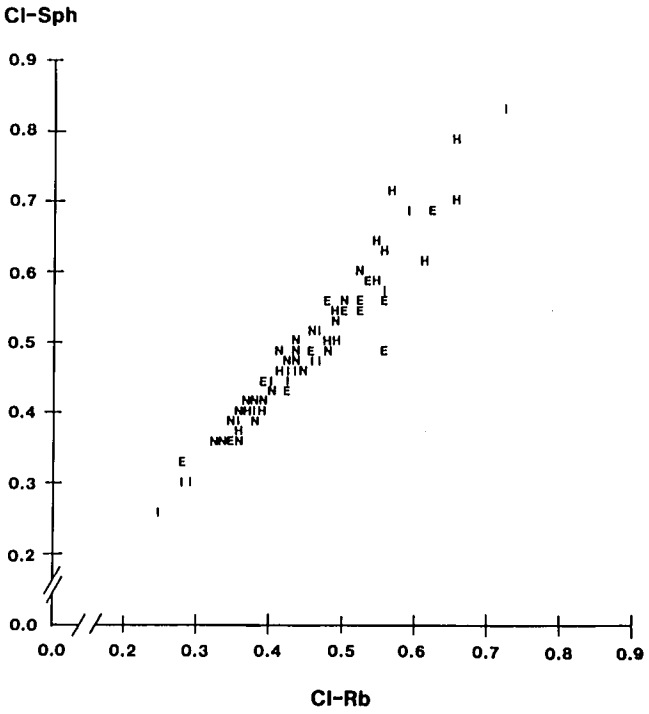

FIG. 1. Plot of clearance of 9-μm spheres (Cl-Sph in $ml \cdot min^{-1} \cdot g^{-1}$) against rubidium clearance (Cl-Rb in $ml \cdot min^{-1} \cdot g^{-1}$). N, H, E, and I represent values observed during nitrous oxide, halothane, enflurane, and isoflurane, respectively. r = 0.97, $P < 0.0001$; Cl-Sph = −0.017 + 1.121 × Cl-Rb.

Results

The amount of activity found in the intestinal segment and mesenteric venous blood did not differ from the injected activity by more than 10%. The difference in the activity of ^{141}Ce and ^{86}Rb (calculated per gram of tissues) between samples of one intestinal loop never exceeded 10%. A very strong and significant correlation was found between rubidium and microsphere clearances, r = 0.97, $P < 0.0001$ (fig. 1).

During each stage of measurements, analysis of arterial blood samples showed Pa_{O_2} to be above 100 mmHg, Pa_{CO_2} between 35 and 40 mmHg, and hematocrit values between 30 and 35%. Observations with values not within these ranges were excluded from the study.

The main variables observed during various conditions of the experiments are presented in table 1. Nitrous oxide anesthesia was accompanied by significantly lower F, Cl-Rb, Cl-Sph, and higher VR values than pentobarbital anesthesia.

One MAC of halothane anesthesia was accompanied by a significantly lower arteriovenous oxygen content

TABLE 1. Circulation in Isolated Intestinal Segment during Inhalation Anesthesia (mean ± SE)

	Pent	N_2O	1I-1	1I-2	E-1	E-2	1-1	1-2	1-2abl
F	0.56 ± 0.01	0.49 ± 0.01*	0.51 ± 0.03	0.70 ± 0.09*†‡	0.50 ± 0.04	0.58 ± 0.02†‡	0.44 ± 0.03*	0.38 ± 0.02*†§¶	0.68 ± 0.08*†**
VR	243 ± 6.0	286 ± 8.5*	269 ± 19.3	198 ± 12.9*†‡	283 ± 27.3*	235 ± 11.7†	317 ± 24.8*	352 ± 28.0*†§¶	207 ± 23.6†**
$AVDO_2$	3.64 ± 0.10	3.79 ± 0.14	2.38 ± 0.24*†	1.41 ± 0.23*†‡	2.21 ± 0.46*†	1.28 ± 0.24*†‡	2.59 ± 0.19*†	2.50 ± 0.28*†§¶	1.34 ± 0.19*†**
O_2 upt	2.0 ± 0.0	1.8 ± 0.1	1.2 ± 0.1*†	0.9 ± 0.1*†‡	1.0 ± 0.1*†	0.7 ± 0.1*†	1.1 ± 0.0*†	0.9 ± 0.1*†	0.9 ± 0.0*†
Cl Rb	0.47 ± 0.01	0.41 ± 0.01*	0.45 ± 0.02	0.57 ± 0.02*†‡	0.43 ± 0.04	0.51 ± 0.02†‡	0.39 ± 0.02*	0.35 ± 0.02*†‡§¶	0.55 ± 0.05*†**
Cl Sph	0.52 ± 0.01	0.45 ± 0.02*	0.49 ± 0.03	0.63 ± 0.03*†‡	0.47 ± 0.04	0.52 ± 0.02†‡	0.41 ± 0.02*	0.37 ± 0.02*†§¶	0.60 ± 0.07*†**
MAP	130 ± 4.1	133 ± 3.1	73 ± 4.0*†	36 ± 5.4*†‡	66 ± 6.2*†	37 ± 4.4*†‡	87 ± 6.9*†	49 ± 5.0*†‡	32 ± 4.7*†**

F = flow in $ml \cdot min^{-1} \cdot g^{-1}$; VR = vascular resistance in the intestinal segment in $dyn \cdot s \cdot cm^{-5} \cdot g$; $AVDO_2$ = arteriovenous blood oxygen content difference in Ml/dl; O_2 upt = oxygen uptake in ml of oxygen $\cdot min^{-1} \cdot 100\ g^{-1}$; Cl Rb and Cl Sph = rubidium clearance and microsphere clearance, respectively, in $ml \cdot min^{-1} \cdot g^{-1}$; MAP = mean aortic pressure in the dog in mmHg (perfusion pressure of the intestinal loop was maintained constant at 100 mmHg); Pent = pentobarbital anesthesia; N_2O = nitrous oxide 66% inspired; H-1 and H-2 = 1 and 2 MAC of halothane anesthesia, respectively; E-1 and E-2 = 1 and 2 MAC of enflurane anesthesia, respectively; I-1 and I-2 = 1 and 2 MAC of isoflurane anesthesia, respectively; I-2abl = 2 MAC of isoflurane with α-adrenoceptor blockade with phentolamine 1 $mg \cdot kg^{-1}$.

* $P < 0.05$ *versus* pentobarbital.
† $P < 0.05$ *versus* N_2O.
‡ $P < 0.05$ *versus* 1 MAC of the same inhalational anesthetic.
§ $P < 0.05$ *versus* corresponding level of halothane.
¶ $P < 0.05$ *versus* corresponding level of enflurane.
** $P < 0.05$ *versus* 2 MAC of isoflurane.

difference ($AVDO_2$) and oxygen uptake by the intestinal segment than the pentobarbital or nitrous oxide anesthesia. Two MAC of halothane anesthesia led to a further decrease in $AVDO_2$ ($P < 0.05$) and oxygen uptake ($P < 0.05$). Vascular resistance in the intestinal loop was significantly lower; blood flow, rubidium, and microsphere clearances were significantly higher than values observed during pentobarbital, nitrous oxide, or 1 MAC of halothane anesthesia (table 1; figs. 2–5).

Enflurane anesthesia, similar to halothane, was accompanied by a significant decrease in $AVDO_2$ and oxygen uptake when compared with pentobarbital and nitrous oxide anesthesia. However, at 2 MAC of enflurane anesthesia, vascular resistance and blood flow did not differ significantly from pentobarbital or 2 MAC of halothane, while blood flow, microsphere, and rubidium clearances were higher and VR lower than during nitrous oxide (table 1, figs. 2–5). In addition, at 2 MAC of enflurane, blood flow and clearances were significantly higher than during 1 MAC of enflurane anesthesia.

Similar to halothane and enflurane, isoflurane also led to a substantial decrease in $AVDO_2$ and oxygen uptake. At 2 MAC of isoflurane, $AVDO_2$ values were significantly lower than during pentobarbital and nitrous oxide but higher than during 2 MAC of halothane or enflurane anesthesia. However, contrary to halothane and enflurane, even 1 MAC of isoflurane anesthesia was associated with a significantly higher vascular resistance and lower blood flow and microsphere and rubidium clearances than pentobarbital anesthesia. During 2 MAC of isoflurane anesthesia, values of vascular resistance were significantly higher, and values of blood flow, rubidium and microsphere clearances were significantly lower than corresponding values observed during 2 MAC of halothane and enflurane anesthesia. During isoflurane anesthesia, a decrease in mean values of oxygen uptake was accompanied by an increase in mean values of VR and a decrease in mean values of F, Cl-Rb, and Cl Sph; however, the coefficients of correlation between the absolute values of oxygen uptake and VR, F, and clearances were low (0.07–0.24) and insignificant ($P > 0.6$).

Additional experiments were performed to elucidate the mechanisms of an increase in vascular resistance caused by isoflurane. Two MAC of isoflurane anesthesia given under conditions of α-adrenoceptor blockade (phentolamine 1 $mg \cdot kg^{-1}$) was accompanied by a decrease in oxygen uptake, similar to the decrease observed during 2 MAC of isoflurane anesthesia *per se,* suggesting that tissue saturation with isoflurane was similar in both conditions: 2 MAC of isolfurane and 2 MAC of isoflurane in conjunction with phentolamine. α-Adrenoceptor blockade abolished vasoconstriction caused by 2 MAC of isoflurane: during 2 MAC of isoflurane combined

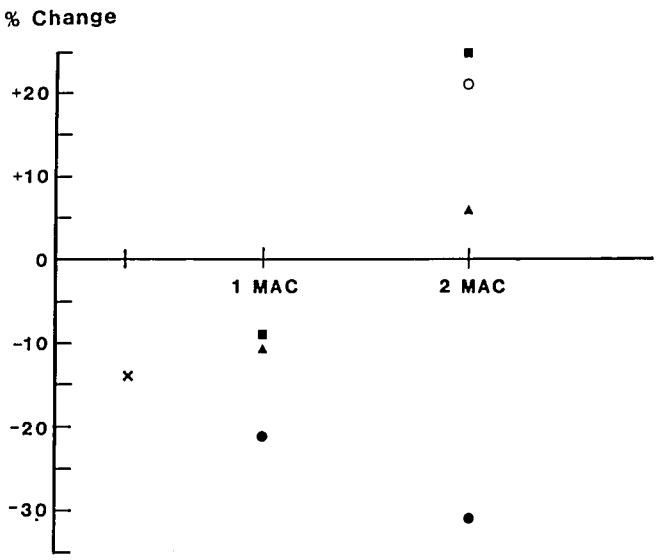

FIG. 2. Per cent change in blood flow through intestinal segment. Depicted symbols represent per cent difference between values observed during pentobarbital (zero line) and nitrous oxide (×), halothane (■), enflurane (▲), and isoflurane (●), respectively; open circles (○) represent isoflurane with α-adrenoceptor blockade. The absolute values and SE of the variables with significance of differences between groups and levels of anesthesia are presented in table 1.

with phentolamine, VR and $AVDO_2$ were significantly lower and F, rubidium, and microsphere clearances were significantly higher than corresponding values observed at 2 MAC of isoflurane without blockade (table 1, figs. 2–5).

Discussion

Rubidium clearance was chosen for the experiments as an index of nutritive flow.[14,20] Rubidium is highly diffusable across exchange vessels, which means that most of the substance presented in the exchange vessels is absorbed by tissues. Consequently, the ratio of absorbed to nonabsorbed rubidium represents the ratio of the blood flow through nutritive vessels to flow through nonnutritive vessels. Previous studies have demonstrated in some pathophysiologic conditions that 9-μm spheres and rubidium behave in the vascular bed in a similar way, *i.e.*, spheres are trapped and rubidium is absorbed in the nutritive exchange vessels and shunted through nonnutritive vessels where exchange does not occur, or occurs to a limited extent.[14] The results of the present study (a strong correlation between microspheres and rubidium clearances) confirm that 9-μm spheres can be used as a tool to study nutritive blood flow in tissues also during inhalation anesthesia.

The perfusion of the intestinal segment by a pump with constant pressure assured independence of the intestinal circulation from the systemic circulation, while

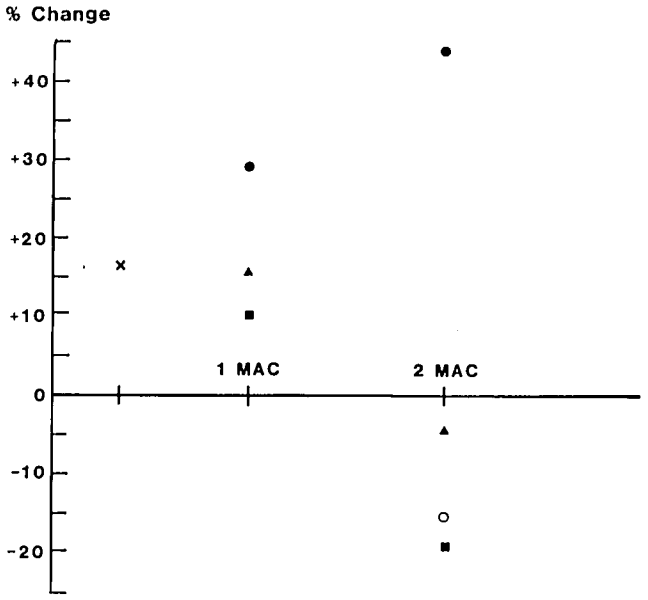

FIG. 3. Per cent change in vascular resistance. See legend to figure 2.

complete isolation of the segment assured independence of the intestinal circulation from nervous regulating mechanisms. Thus, this preparation allowed us to study the direct influence of anesthetics on the intestinal circulation in conjunction with some indirect effects related to various hormonal factors, *e.g.*, epinephrine, histamine, *etc.*

Experiments involving laparotomy and isolated intestinal loop preparation could not be performed without anesthesia; therefore, an anesthetic that would serve as a control was selected in order to evaluate the effects of inhalation anesthetics in question. Pentobarbital de-

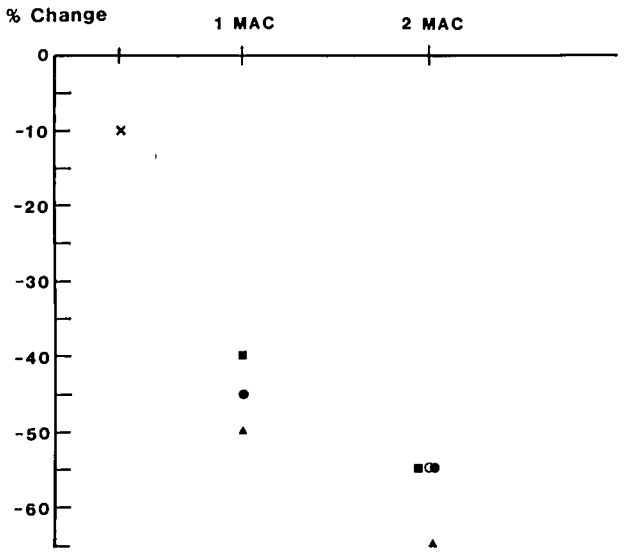

FIG. 4. Per cent change in oxygen uptake. See legend to figure 2.

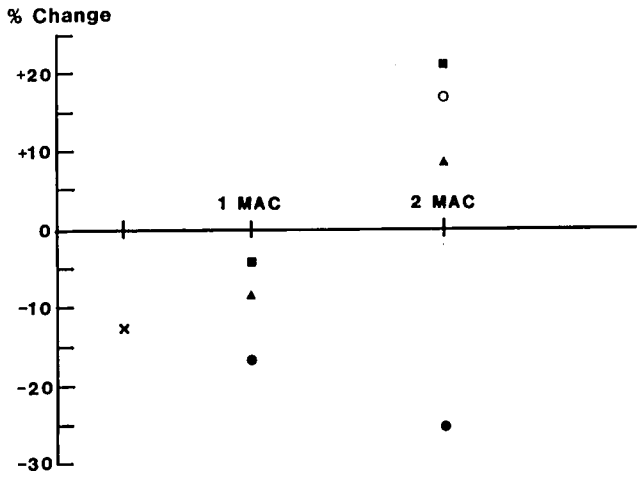

FIG. 5. Per cent change in rubidium clearance. See legend to figure 2.

creases intestinal blood flow in dogs[21,22] but to a much lesser extent than other studied anesthetics.[23] Therefore, pentobarbital was chosen for the control group of animals. In the experimental group, methohexital, a barbiturate with a relatively short half-life,[24] was selected for induction of anesthesia. Barbiturates can decrease MAC values of inhalational anesthetics for a long time.[25] It must be kept in mind that methohexital and nitrous oxide had certain residual effects on the following stages of the experiment, but the effects were probably minimal and, more important, all three groups of animals receiving inhalational anesthetics apparently experienced similar residual effects of methohexital and nitrous oxide. All of the animals had the same fluid management, surgical preparation, and similar hematocrit values, which probably means that animals had similar sympathetic stimulation throughout the experiments. Therefore, differences between groups can be attributed to the influence of the anesthetic resulting from the following: the anesthetic's direct effect on the intestinal circulation, and/or from the anesthetic's effect on hormonal factors (*e.g.*, release of epinephrine from adrenal glands).

Total blood flow, determined directly, and nutritive flow, evaluated indirectly by Cl-Rb and Cl-Sph, were lower during nitrous oxide than pentobarbital anesthesia (table 1, figs. 2, 5). The observed vasoconstriction can be related to the direct influence of nitrous oxide or to an increase in the concentration of vasoconstricting substances (*e.g.*, catecholamines), which resulted from the influence of nitrous oxide on adrenal glands and/or from light anesthesia. Nitrous oxide anesthesia in the whole animal was accompanied by a decrease in blood flow through the preportal area[11,26] and an increase in mesenteric vascular resistance.[26] These changes in splanchnic circulation (described in the literature and also observed in this study) may be the result of an increase in catecholamine levels observed during nitrous oxide anesthesia.[27] Therefore, our results in this regard supplement previously reported data.

Halothane, enflurane, and isoflurane anesthesia were accompanied by a much lower $AVDO_2$ and oxygen uptake than pentobarbital and nitrous oxide. It appears that the decrease in oxygen uptake by these inhalational agents depends on the direct influence of anesthetics on metabolism. It has to be realized that the effect of inhalational anesthetics on intestinal oxygen uptake was compared with the effect of pentobarbital and nitrous oxide rather than with the awake state. The three studied inhalational anesthetics affected intestinal circulation differently: compared with pentobarbital, enflurane anesthesia was not accompanied by remarkable differences in VR, nutritive blood flow (evaluated by Cl-Rb and Cl-Sph), and total blood flow (measured directly); halothane at 2 MAC decreased VR and increased total and nutritive blood flow (Cl-Rb increased), while isoflurane increased VR and decreased total and nutritive blood flow through the intestinal segments.

During halothane anesthesia, mesenteric vascular resistance in the whole body was unchanged[5,9] or increased,[7] while mesenteric blood flow always decreased.[4-11] Obviously, changes in mesenteric vascular resistance in the whole body depend not only on direct and humorally mediated factors but on changes in primary systemic circulatory variables and nervous control. A decrease in intestinal blood flow usually is associated with a reduction in cardiac output during barbiturate[12] and halothane[13] anesthesia. Thus, it appears that the direct effect of halothane at 2 MAC is vasodilation, while in the whole body a decrease in cardiac output leads to a compensatory increase in mesenteric vascular resistance and a decrease in blood flow. Apparently, direct vasodilatory action of halothane does not seem to interfere with this vasoconstricting response.

Isoflurane led to an increase in VR and a decrease in flow, total and nutritive. Phentolamine completely abolished the vasoconstricting effect of isoflurane. It is well-known that regional blood flow is controlled mainly by local metabolic factors.[2] Isoflurane, as well as halothane and enflurane, reduced oxygen demand of the intestinal loop. An autoregulatory-mediated increase in resistance and a decrease in flow followed the decrease in oxygen uptake only during isoflurane but not during halothane and enflurane anesthesia. The data could have suggested that this metabolic autoregulation was preserved during isoflurane and lost during enflurane (blood flow did not change) and especially during halothane anesthesia (blood flow even increased). However, a statistical analysis

showed that a reduction in oxygen uptake during isoflurane anesthesia did not correlate at all with the changes in resistance, flow, and clearances. Therefore, the data do not support the "autoregulatory" explanation of the constricting effect of isoflurane on the intestinal vasculature. On the other hand, disappearance of the isoflurane-induced vasoconstriction in conditions of α-adrenoceptor blockade suggests that the effect is mediated through circulating catecholamines. Evidence concerning the influence of isoflurane on catecholamines is conflicting but suggests some sympathoadrenal stimulation.[28,29] Preganglionic sympathetic activity is inhibited to a lesser extent than vagal activity during isoflurane anesthesia,[30] suggesting that the increase in circulating catecholamines might result from the relatively high preganglionic sympathetic activity. The reported effects of isoflurane on plasma catecholamines are not consistent within the literature. Perry *et al.* did not observe an increase in catecholamines during isoflurane anesthesia.[31] Dobkin *et al.* observed increased catecholamine levels during isoflurane anesthesia.[32] Additionally, a significant increase in plasma epinephrine and a decrease in the concentration of norepinephrine also has been demonstrated clearly, suggesting that the increase in plasma epinephrine results from an action of isoflurane on adrenal epinephrine release.[33] Our study employed extensive surgical preparation, which alone could result in a substantial release of catecholamines. Thus, it seems that the direct influence of isoflurane on the intestinal vasculature is vasodilation, which is overridden by the vasoconstricting effect of circulating catecholamines. Apparently, catecholamine concentration did not increase during halothane and enflurane, as it did during isoflurane anesthesia.

It appears that effects of isoflurane on regional circulation are rather complex: It dilates cerebral and coronary vessels disproportionally to the metabolic needs of the brain[34] and the myocardium,[35,36] it dilates hepatic arterial vasculature and increases hepatic arterial blood flow despite a decrease in blood pressure and cardiac output,[11,13] and it constricts intestinal vasculature in the whole body,[11,13,36] as well as in the isolated intestinal loop preparation (present study).

In summary, compared with pentobarbital anesthesia, halothane, enflurane, and isoflurane decreased oxygen uptake in the intestinal segment, probably influencing tissue metabolism. Enflurane did not significantly influence the intestinal vascular tone; halothane at 2 MAC decreased vascular resistance and increased total and nutritive blood flow, while isoflurane increased vascular resistance and decreased total and nutritive blood flow. The data suggest that this increase in VR was mediated via catecholamines. Decreases in mesenteric blood flow, which always have been observed during anesthesia with these agents, is related mainly to the indirect effects of anesthetics mediated through changes in systemic circulation and the central nervous system.

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References

1. Hickey RF, Eger EI II: Circulatory effects of inhaled anaesthetics, The Circulation in Anaesthesia. Applied Physiology and Pharmacology. Edited by Prys-Roberts C London, Blackwell Scientific Publications, 1980, pp 441–457
2. Granger DN, Richardson PDI, Kvietys PR, Mortillaro NA: Intestinal blood flow. Gastroenterology 78:837–863, 1980
3. Gelman S, Reves JG, Harris D: Circulatory responses to midazolam anesthesia: Emphasis on canine splanchnic circulation. Anesth Analg 62:135–139, 1983
4. Gelman S: The effect of enteral oxygen administration on the hepatic circulation during halothane anaesthesia: Experimental investigations. Br J Anaesth 47:1253–1259, 1975
5. Thulin L, Andreen M, Irestedt L: Effect of controlled halothane anaesthesia on splanchnic blood flow and cardiac output in the dog. Acta Anaesthesiol Scand 19:146–153, 1975
6. Andreen M, Irestedt L, Zetterstrom B: The different responses of the hepatic arterial bed to hypovolaemia and to halothane anaesthesia. Acta Anaesthesiol Scand 21:457–469, 1977
7. Ahlgren I, Aronsen F, Bjorkman I, Wetterlin S: The hemodynamic effect of halothane in the normovolemic dog. Acta Anaesthesiol Scand 22:83–92, 1978
8. Irestedt I, Andreen M: Effects of enflurane on haemodynamics and oxygen consumption in the dog with special reference to the liver and preportal tissues. Acta Anaesthesiol Scand 23:13–26, 1979
9. Hughes RL, Mathie RT, Fitch W, Campbell D: Effects of enflurane and halothane on liver blood flow and oxygen consumption in the greyhound. Br J Anaesth 52:1079–1086, 1980
10. Tranquilli WJ, Manohar M, Parks CM, Thurmon JC, Theodorakis MC, Benson GJ: Systemic and regional blood flow distribution in unanesthetized swine and swine anesthetized with halothane + nitrous oxide, halothane, or enflurane. ANESTHESIOLOGY 56:369–379, 1982
11. Lundeen G, Manohar M, Parks C: Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with and without 50% nitrous oxide. Anesth Analg 62:499–512, 1983
12. Bulkley GB, Kvietys PR, Perry MA, Granger DN: Effects of cardiac tamponade on colonic hemodynamics and oxygen uptake. Am J Physiol 244:G604–612, 1983
13. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. ANESTHESIOLOGY 61:84–88, 1984
14. Gelman S, Granger DN, Fowler K, Smith LR: Clearance of 9 μm spheres and Rb in the intestinal circulation. Am J Physiol 247:G13–G18, 1984
15. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM: Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 20:55–79, 1977
16. Gelman S, Reves JG, Fowler K, Samuelson PN, Lell WA, Smith

LR: Regional blood flow during cross-clamping of the thoracic aorta and infusion of sodium nitroprusside. J Thorac Cardiovasc Surg 85:287–291, 1983

17. Baer RW, Payne BD, Verrier ED, Vlahakes GJ, Molodowitch D, Uhlig PN, Hoffman JIE: Increased number of myocardial blood flow measurements with radionuclide-labeled microspheres. Am J Physiol 246:H418–H434, 1984
18. Snedecor GW, Cochran WG: Statistical Methods, seventh edition. Ames, The Iowa State University Press, 1980, pp 215–269
19. SAS Institute Inc: SAS User's Guide: Statistics. Cary, SAS Institute Inc. 1982, pp 113–199
20. Shepherd AP: Intestinal capillary exchange capacity and oxygen uptake rate: Applications of indicator dilution principles, Measurements of Blood Flow: Applications to the Splanchnic Circulation. Edited by Grager DN, Bulkley GB. Baltimore, Williams and Wilkins, 1981, pp. 293–317
21. Katz ML, Bergman EN: Simultaneous measurements of hepatic and portal venous blood flow in the sheep and dog. Am J Physiol 216:946–952, 1969
22. Sjostrom B, Wulff KE: Influence of long-term anesthesia on regional blood flow distribution and hemodynamics in the dog. Eur Surg Res 7:1–9, 1975
23. Kvietys PR, Barrowman JA, Granger DN: Effects of anesthetics and other experimental conditions on splanchnic blood flow, Measurements of Blood Flow, Applications to the Splanchnic Circulation. Edited by Ganger DN, Bulkley BG. Baltimore, Williams and Wilkins, 1981, pp 57–65
24. Hudson RJ, Stanski DR, Burch PG: Pharmacokinetics of methohexital and thiopental in surgical patients. ANESTHESIOLOGY 59:215–219, 1983
25. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. ANESTHESIOLOGY 26:756–763, 1965
26. Thomson, IA, Fitch HW, Campbell D: Effects of nitrous oxide on liver haemodynamics and oxygen consumption in the greyhound. Anaesthesia 37:548–553, 1982
27. Smith NT, Eger EI II, Stoelting RK, Whayne TF, Cullin D, Kadis LB: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. ANESTHESIOLOGY 32:410–421, 1970
28. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespear TJ, Bahlman SH: The cardiovascular effects of a new inhalational anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971
29. Horan BF, Prys-Roberts C, Roberts JG, Bennett MJ, Foex P: Haemodynamic responses to isoflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol. Br J Anaesth 49:1179, 1977
30. Skovsted P, Sapthavichaikul S: The effects of isoflurane on arterial pressure, pulse rate, autonomic nervous activity, and barostatic reflexes. Can Anaesth Soc J 24:304–314, 1977
31. Perry LB, Van Dyke RA, Theye RA: Sympathoadrenal and hemodynamic effects of isoflurane, halothane, and cyclopropane in dogs. ANESTHESIOLOGY 40:465–470, 1974
32. Dobkin AB, Byles PH, Arandia HY, Ghanooni S, Nishiolka K, Levy AA: Comparative metabolic response to halogenated anaesthetics. Acta Anaesthesiol Scand 16:69–75, 1972
33. Balasaraswathi K, Glisson SN, El-Etr AA, Mummaneni N: Haemodynamic and catecholamine response to isoflurane anaesthesia in patients undergoing coronary artery surgery. Can Anaesth Soc J 29:533–537, 1982
34. Newberg LA, Michenfelder JD: Cerebral protection by isoflurane during hypoxemia or ischemia. ANESTHESIOLOGY 59:29–35, 1983
35. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H: Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. ANESTHESIOLOGY 59:91–97, 1983
36. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557–565, 1984