Anesthesiology
76:402–408, 1992

Effects of Hypoxemia on Regional Blood Flows during Anesthesia with Halothane, Enflurane, or Isoflurane

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Hypoxemia during anesthesia can cause severe morbidity and mortality. To determine how the volatile anesthetics alter the normal hemodynamic compensation for hypoxemia, we investigated the effects of various anesthetics on regional blood flows during normoxemia and during normocapnic hypoxemia ($F_{I_{O_2}}$ 0.12 for 20 min) in rats. Using the radioactive microsphere method, organ blood flows were determined in animals anesthetized with 1 MAC of halothane, enflurane, or isoflurane and in awake animals. Brain blood flow increased significantly with hypoxemia in awake animals. However, brain blood flow decreased in all anesthetized animals that were hypoxemic. Coronary blood flow also increased significantly with hypoxemia in awake animals. In the presence of volatile anesthetics, coronary blood flow decreased, a decrease that was unchanged with hypoxemia. Thus, there was a large difference in brain and coronary blood flows between awake hypoxemic and anesthetized hypoxemic animals. Hypoxemia did not alter the magnitude of renal, gastrointestinal tract, or total hepatic blood flows in awake animals. However, all three blood flows decreased significantly in anesthetized hypoxemic animals. We conclude that volatile anesthetics modify the compensatory responses to hypoxemia that occur in awake animals, resulting in decreased blood flow to vital organs. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Brain: cerebral blood flow. Hypoxemia. Measurement techniques, regional blood flow: radioactive microspheres.)

GENERAL ANESTHESIA has a variety of direct and indirect effects on cellular function and cell viability after hypoxemia or ischemia. *In vitro* studies have demonstrated differences among anesthetics in their effects on cellular metabolism.[1] However, not only is cellular function affected by anesthetics, but the distribution of blood flow (and thus oxygen transport) to various organs is changed as well.[2] We reported previously that anesthetics have significant and specific effects on regional blood flows during hypovolemia.[3]

In this study, we investigated the effects of anesthetics on regional blood flows during hypoxemia. We determined systemic cardiovascular parameters, as well as regional blood flow rates, to several systemic organs in rats anesthetized with halothane, enflurane, or isoflurane and compared these results to those obtained in awake animals. Initial determinations were made during normoxic conditions, and the results were compared with those obtained while the animals breathed an hypoxic gas mixture. We attempted to answer the following questions: 1) Are there differences in the peripheral vascular responses to hypoxemia between awake and anesthetized animals? and 2) are there differences in the responses to hypoxemia among the inhalation anesthetics?

Materials and Methods

The experimental design included eight groups of six rats each. Normoxemic and hypoxemic animals were studied while receiving one of three anesthetics: halothane, enflurane, or isoflurane. Similar data were obtained in awake animals. Arterial carbon dioxide tension and body temperature were controlled, and systemic and regional hemodynamic parameters were measured. These experiments conformed to the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiologic Society, and the protocols were approved by the Animal Care Committee of the University of Virginia.

Male Sprague-Dawley rats (Charles River Laboratories), 9–12 weeks old, weighing 370 ± 6 g were studied. All animals were kept on a diet of standard rat chow and water *ad libitum* until the day of the experiment. The animals receiving anesthesia were prepared as follows. Animals were randomized into three groups and anesthetized with the anesthetic to be studied, in an inspired concentration reported to represent 1 MAC for male Sprague-Dawley rats of this age,[4,5] *i.e.*, halothane, 1.1%; isoflurane, 1.4%; or enflurane, 2.2%. Polyethylene (PE-50) catheters were inserted in the left femoral artery for continuous blood pressure recording and arterial blood sampling, and in the left femoral vein for infusion. Another PE-50 catheter was heated and drawn to PE-10 size; this catheter was inserted *via* the right carotid artery into the left cardiac ventricle for injection of microspheres.

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Received from the Department of Anesthesiology, University of Virginia, Charlottesville, Virginia. Accepted for publication October 31, 1991. Supported by National Institutes of Health grant GM35933. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, 1988.

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Correct placement was verified by observation of the pressure waveform recorded during insertion of the catheter. A tracheostomy was performed; animals were paralyzed with pancuronium bromide, 1 mg/kg intravenously; and ventilation was controlled with a small animal ventilator (Harvard Apparatus), using an inspired oxygen fraction (FI_{O_2}) of 0.3. Rectal temperature was measured and controlled between 36° and 38° C by a heating lamp. An intravenous infusion with 0.9% NaCl solution, 1.5 ml/h, was maintained throughout.

After vascular and airway access were established, the animals were allowed to stabilize for 75 min, during which time two arterial blood samples were analyzed for *p*H, Pa_{O_2}, and Pa_{CO_2}. The ventilator was adjusted to maintain the Pa_{CO_2} between 30 and 35 mmHg.

The preparation was generally similar for awake animals. These rats were briefly anesthetized with isoflurane, 1.4–1.9% inspired, for placement of the vascular catheters. Wounds were coated with lidocaine gel (1%) and closed. Tracheostomy was not performed, and the animals were gently restrained in a rat restraining cage (Braintree Scientific). Anesthesia was then discontinued, and an infusion of 0.9% NaCl solution, 1.5 ml/h, was begun. The restraining cage was then placed in a Plexiglas chamber. Movement and noise in the area were curtailed to minimize sensory stimuli. A period of 2 h was allowed to permit full recovery from anesthesia.

In animals to be studied under hypoxemic conditions, the FI_{O_2} was then decreased to 0.12 for a period of 20 min. In normoxic animals, the FI_{O_2} was maintained at 0.3 for anesthetized animals and 0.21 for awake animals. (These FI_{O_2} values were selected to produce similar Pa_{O_2} values, based on data from our previous experiments in rats.) Systemic and cerebral blood flows were determined by the radiolabeled microsphere technique in all rats. Approximately 400,000 ^{141}Ce-labeled microspheres, 15 ± 1 μm in diameter, in 0.2 ml suspending solution (NaCl 0.9% and Tween-80 0.01%), were thoroughly stirred and injected into the left cardiac ventricle. The catheter was flushed with 0.4 ml of 0.9% NaCl. Arterial blood, withdrawn at a rate of 0.5 ml · min^{-1} for 10 s before and for 60 s after the injection of microspheres, was used as a reference sample. Thereafter, a final arterial blood sample was obtained for determination of Pa_{O_2}, Pa_{CO_2}, *p*H, and hematocrit, and the animal was killed by intravenous injection of KCl.

The brain was then removed from the skull. Thereafter, the heart, lungs, liver, spleen, stomach, small intestine, cecum, large intestine and kidneys were dissected also. The position of the cardiac catheter in the left ventricle was verified by direct observation. Similar blood flow rates in the left and right kidneys were used as a criterion for adequate mixing of microspheres; differences of more than 20% indicated insufficient mixing, and data from those animals were not included in the analysis. Measurement of radioactivity in the lungs was used to ascertain the absence of left-to-right shunting, perforation of the ventricular septum, or migration of microspheres through systemic capillary beds.

Radioactivity of organs and reference samples was measured in a well-type γ counter (Compugamma 1282-002, LKB Instruments Inc.). Cardiac output (ml · min^{-1}) was calculated from the equation:

$$\text{cardiac output} = \frac{\text{total injected activity} \times \text{reference sample flow}}{\text{reference sample activity}}$$

Total injected activity was determined by counting radioactivity in the syringe before and after injection of the microspheres. Systemic vascular resistance (SVR) was calculated as:

$$\text{resistance} = \frac{\text{mean arterial pressure}}{\text{cardiac output}}$$

and is reported as mmHg · ml^{-1} · min. Regional blood flows were calculated from the equation:

$$\text{flow} = \frac{\text{organ activity} \times \text{reference sample flow}}{\text{reference sample activity}}$$

and are reported as ml · min^{-1} · 100 g^{-1}. Vascular resistance of organs draining into the central venous system was calculated as:

$$\text{resistance} = \frac{\text{MAP}}{\text{organ blood flow}}$$

and is reported as mmHg · ml^{-1} · min · g. Central venous pressure was assumed to be zero, and thus perfusion pressure was assumed to equal mean arterial pressure (MAP) in these organs. Pressure in the portal system was assumed to be 10 mmHg, and therefore the formula:

$$\text{resistance} = \frac{\text{MAP} - 10}{\text{organ blood flow}}$$

was used to calculate resistances in the spleen, stomach and intestines.

The approach of Ross and Daggy[6] was used for calculating liver blood flows. Radioactivity in the liver was assumed to represent hepatic arterial flow, whereas portal venous flow was calculated as the sum of blood flow through the spleen, stomach, and intestines. Total hepatic flow was calculated by adding hepatic arterial and portal venous flows.

All data are reported as mean ± standard error of the mean. One-way analysis of variance was used to test for intragroup differences (awake *vs.* halothane *vs.* enflurane *vs.* isoflurane) among normoxic animals, among hypoxic animals groups, and between normoxia *versus* hypoxia for

each anesthetic condition. If significant, this was followed by a least-significant-difference multiple range test to compare specific groups. $P < 0.05$ was considered significant.

Results

The results for arterial blood gases are reported in table 1. Pa_{CO_2} values were similar in all animals. Pa_{O_2} values were similar in all normoxic animals (87 ± 4 mmHg) and in all hypoxemic animals (36 ± 1 mmHg). Whereas hypoxemia did not change *p*H significantly in awake animals, arterial *p*H decreased during hypoxemia in animals anesthetized with halothane, enflurane, or isoflurane.

Cardiovascular data are reported in table 2. MAP, cardiac output, and SVR were not altered by hypoxemia in the awake group. However, MAP and cardiac output were significantly decreased in all anesthetized hypoxemic animals. SVR was unchanged in the anesthetized hypoxemic animals as compared with awake hypoxemic animals.

Cerebral blood flow changes are depicted in figure 1. Hypoxemia increased cerebral blood flow by 102 ± 18% in awake animals. The volatile anesthetics also increased cerebral blood flow during normoxemia. However, compared with awake hypoxemia, cerebral blood flow decreased an average of 64 ± 6% during hypoxemic anesthesia. Among the various anesthetics, the decrease with enflurane was significantly greater than with isoflurane.

Coronary blood flows are shown in figure 2. Hypoxemia increased coronary blood flow by 125 ± 22% in awake animals. All three volatile anesthetics decreased coronary blood flow significantly during normoxemia. Hypoxemia during anesthesia yielded coronary blood flows similar to those during normoxic anesthesia. Compared with awake hypoxemia, coronary blood flow decreased an average of 73% ± 7% during hypoxemic anesthesia.

Renal blood flow data are reported in figure 3. Hypoxemia did not alter renal blood flow in awake animals. Renal blood flow decreased during normoxemia in the presence of 1 MAC halothane, whereas it was unchanged during enflurane or isoflurane. Renal blood flow during hypoxemic anesthesia decreased similarly for all anesthetics (63 ± 7%) when compared with awake hypoxemia.

Gastrointestinal (GI) tract blood flows are shown in figure 4. Hypoxemia did not alter GI tract blood flow in awake animals. Halothane decreased GI blood flow in normoxic animals, but enflurane and isoflurane did not. In the presence of hypoxemia, the three volatile anesthetics decreased GI blood flow 52 ± 11% compared with awake hypoxemia.

Total liver blood flows are depicted in figure 5. Hypoxemia did not alter total hepatic blood flow in awake animals. Likewise, no anesthetic altered total liver flow during normoxemia. However, total liver blood flow decreased similarly for all anesthetics, an average of 62 ± 10% during hypoxemia when compared with awake animals.

Organ vascular resistances are presented in table 3. Hypoxemia significantly decreased the vascular resistance in all organs except the kidneys in awake animals. Vascular resistance during anesthesia plus hypoxemia were similar to awake hypoxemia for all anesthetics and all organs except the brain, where cerebrovascular resistance was less with isoflurane than with enflurane anesthesia.

Discussion

The reference sample microsphere technique has been used extensively to measure regional blood flows. The number of microspheres injected was selected to minimize hemodynamic disturbances,[7] while still providing enough microspheres to accurately measure flow in small tissue samples (unpublished observations from our laboratory).

TABLE 1. Arterial Blood Gas Values

	Awake	Halothane	Enflurane	Isoflurane
Pa_{CO_2} (mmHg)				
Normoxia	36 ± 1	34 ± 2	35 ± 1	35 ± 1
Hypoxemia	36 ± 2	33 ± 1	33 ± 1	34 ± 1
Pa_{O_2} (mmHg)				
Normoxia	89 ± 3	87 ± 3	84 ± 4	91 ± 5
Hypoxemia	39 ± 2[n]	35 ± 1[n]	37 ± 2[n]	34 ± 1[n]
*p*H				
Normoxia	7.41 ± 0.01	7.44 ± 0.01	7.41 ± 0.02	7.37 ± 0.01
Hypoxemia	7.34 ± 0.06[hei]	7.26 ± 0.03[na]	7.27 ± 0.01[na]	7.27 ± 0.03[na]
Hematocrit (%)				
Normoxia	44 ± 1[hei]	37 ± 1[a]	38 ± 1[a]	37 ± 2[a]
Hypoxemia	43 ± 1[hei]	38 ± 1[a]	38 ± 1[a]	37 ± 1[a]

Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

TABLE 2. Cardiovascular Data

	Awake	Halothane	Enflurane	Isoflurane
Cardiac output (ml/min)				
Normoxia	108 ± 9^{h}	79 ± 5^{ia}	96 ± 7	104 ± 9^{h}
Hypoxemia	107 ± 6^{hei}	49 ± 8^{na}	45 ± 4^{na}	55 ± 3^{na}
Systemic vascular resistance (mmHg · ml^{-1} · min)				
Normoxia	1.15 ± 0.14^{ei}	0.94 ± 0.10	0.86 ± 0.12^{a}	0.78 ± 0.02^{a}
Hypoxemia	1.02 ± 0.07	0.90 ± 0.15	0.83 ± 0.05	0.81 ± 0.05
Mean arterial pressure (mmHg)				
Normoxia	121 ± 8^{hei}	73 ± 5^{a}	79 ± 6^{a}	81 ± 7^{a}
Hypoxemia	108 ± 5^{hei}	39 ± 2^{na}	37 ± 4^{na}	44 ± 3^{na}

Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

Several precautions are necessary when using the microsphere technique. First, the right carotid artery is occluded by the catheter. It has been shown that unilateral carotid occlusion results in small but significant differences in blood flow to the right and left cerebral hemispheres during anesthesia in rats.[3] We would expect this effect to be similar in all groups, and therefore, we have reported average flows for structures from both hemispheres. Second, our vascular resistance calculations were based on MAP only, and not on perfusion pressure. In the brain, perfusion pressure may have differed from MAP due to the effect of intracranial pressure, which we did not measure. However, our values for hemodynamic parameters and for cerebral blood flow correspond closely to those reported in other studies, using either microspheres or other techniques.[3,8,9]

Arterial pressure was greater in awake than in anesthetized normoxic rats. We attempted to reduce stress in the awake animals by carefully coating the wounds with lidocaine gel, by covering the restraining cage, and by limiting noise and movement in the environment. Miller *et al.* reported no differences in plasma norepinephrine levels between awake restrained rats and rats anesthetized with halothane or enflurane.[10] Epinephrine levels were similar in awake animals and those anesthetized with halothane also, although plasma epinephrine was less in animals anesthetized with enflurane. It therefore appears unlikely that differences in hemodynamic parameters resulted from immobilization stress in awake animals but rather resulted from the actions of the anesthetics on the circulation. Hematocrit in the awake animals was significantly greater than in anesthetized animals. This may have resulted from differences in blood sampling; only one arterial blood sample was obtained in the awake animals, whereas three samples were obtained from anesthetized rats. However, a possible effect of anesthesia on fluid distribution cannot be eliminated. Whatever the cause, the resultant effect on blood viscosity and oxygen transport could be expected to be of minor importance here.

Awake animals compensated almost completely for the stress of hypoxemia. No changes were observed in *p*H, cardiac output, SVR, or MAP. These findings are similar to those reported by others.[6,11] Marshall and Metcalfe[12]

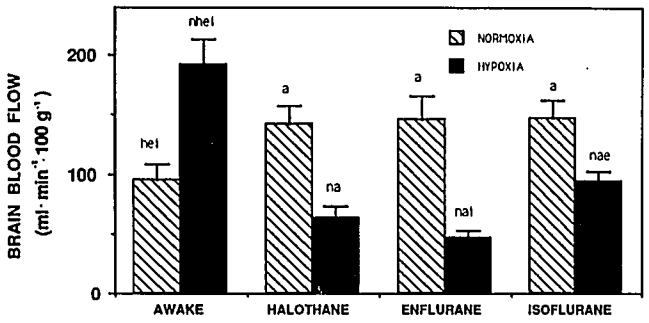

FIG. 1. Global brain blood flow for awake and anesthetized rats. Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

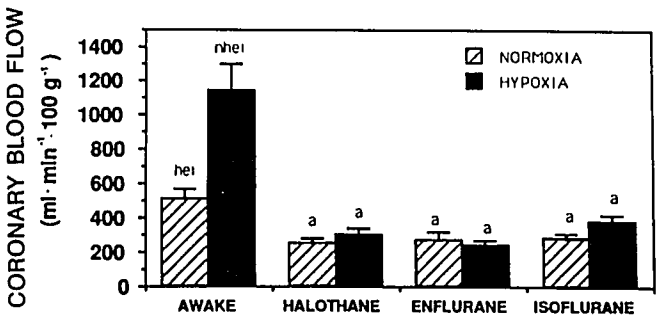

FIG. 2. Coronary blood flow for awake and anesthetized rats. Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

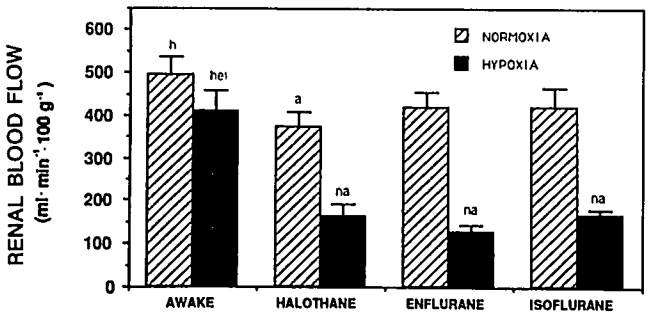

FIG. 3. Renal blood flow for awake and anesthetized rats. Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

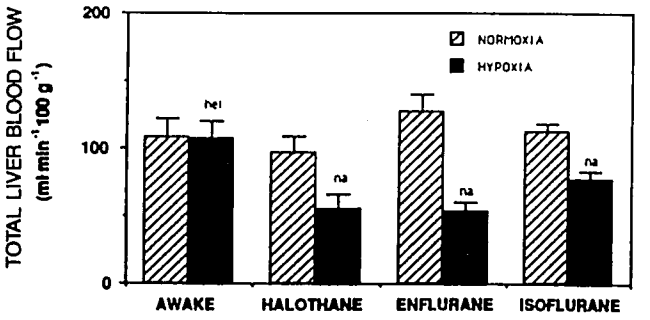

FIG. 5. Total liver blood flow for awake and anesthetized rats. Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

reported a normal blood pressure but an increased cardiac index in acutely hypoxemic rats. In marked contrast to the awake state, we observed significant changes during hypoxemia in anesthetized animals. Arterial *p*H, cardiac output, and MAP decreased during hypoxemia with each of the three anesthetics. The change in MAP resulted from a decrease in cardiac output, whereas SVR remained unaltered. The most likely explanation is myocardial depression by local tissue hypoxia, but causative mechanisms were not evaluated in these studies. The decrease in *p*H in the arterial blood probably resulted from increased anaerobic metabolism in anesthetized rats, especially in response to the decreased cardiac output that accompanied hypoxia in these animals, although no direct indicators of anaerobic metabolism were measured.

Our awake animals breathed spontaneously, whereas in the anesthetized animals the lungs were mechanically ventilated. Positive-pressure ventilation can be associated with a decreased cardiac output and decreased mean arterial pressure. The presumed mechanisms include decreased venous return (most pronounced with hypovolemia), increased pulmonary vascular resistance (resulting from lung inflation), and decreased left ventricular stroke volume. Hypoxemia has been shown to aggravate the hemodynamic dysfunction associated with positive-pressure ventilation.[13] It is possible that hypoxemia and positive-pressure ventilation combined to augment the effects of the anesthetics to produce the decrease in cardiac output and mean arterial pressure during hypoxemic anesthesia. However, the relevance of our observations during hypoxemic anesthésia remains, for it would be unlikely to allow continued spontaneous ventilation in the presence of significant hypoxemia during general anesthesia.

Organ blood flows sorted into two major groups, depending upon the response to hypoxemia in awake animals. The first group included the heart and brain. Blood flows increased to both of these organs during hypoxemia in awake animals. This occurred because of a decrease in vascular resistance in both organs since MAP was similar in the hypoxemic and normoxic animals.

The second group included the abdominal viscera. Kidney, GI tract, and total hepatic blood flows remained unchanged with hypoxemia in the awake animals.

Since cardiac output did not change during awake hypoxemia, it must be assumed that blood flow decreased in some vascular bed(s) to offset the increased flow to the heart and brain. Although not measured in this study, it is possible that flow decreased in the skin rather than muscle, because muscle blood flow has been shown to increase significantly during acute hypoxemia in rats.[12,14]

Oxygen delivery in the rat depends upon blood flow, hemoglobin content, Pa_{O_2}, and the oxyhemoglobin dissociation curve for rat hemoglobin. Because hemoglobin content was similar in all awake animals, and because it can be assumed that the oxyhemoglobin dissociation curve was also similar, then the two factors affecting oxygen delivery were blood flow and Pa_{O_2}. In awake animals, the heart and brain increased blood flow in the presence of

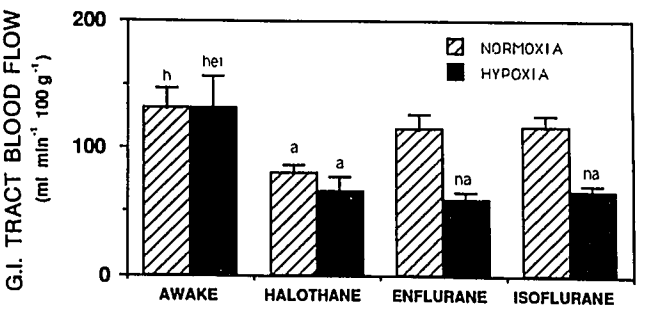

FIG. 4. Total gastrointestinal blood flow for awake and anesthetized rats. Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

TABLE 3. Organ Vascular Resistances (mmHg · ml^{-1} · min · g)

	Awake	Halothane	Enflurane	Isoflurane
Brain				
Normoxia	135 ± 16^{hei}	54 ± 7^{a}	61 ± 11^{a}	56 ± 6^{a}
Hypoxemia	64 ± 6^{n}	63 ± 5	83 ± 11^{i}	47 ± 3^{e}
Heart				
Normoxia	25 ± 3^{e}	28 ± 3	36 ± 8^{a}	29 ± 1
Hypoxemia	10 ± 2^{n}	14 ± 1^{n}	16 ± 1^{n}	13 ± 2^{n}
Kidneys				
Normoxia	26 ± 4	21 ± 4	20 ± 3	20 ± 1
Hypoxemia	28 ± 3	26 ± 3	30 ± 2^{n}	26 ± 1
Gastrointestinal tract				
Normoxia	98 ± 23^{ei}	85 ± 15	64 ± 9^{a}	61 ± 4^{a}
Hypoxemia	63 ± 9^{n}	48 ± 7^{n}	48 ± 7	53 ± 4

Superscripts indicate significant differences ($P < 0.05$) as compared with other groups: n = normoxia; a = awake; h = halothane; e = enflurane; i = isoflurane.

hypoxemia, whereas the other organs did not. Thus the heart and brain appear to have defended oxygen delivery to a greater extent than did other organs during awake hypoxemia. That the brain defends oxygen delivery during hypoxemia has been amply demonstrated.[15–18]

Blood flows to all organs decreased during hypoxemic anesthesia when compared to awake hypoxemia. In all cases, the decrease was the result of a decrease in MAP since vascular resistance remained unchanged.

The direction of blood flow changes during awake hypoxemia in our experiment are similar to those found by Marshall and Metcalfe[12] in rats rendered acutely hypoxemic (FI_{O_2} 8% and 6% for 3 min). Although our absolute percent change differed somewhat from their findings, it must be emphasized that their model (3 min of hypoxemia) is different from ours (20 min of hypoxemia). Their work delineated the arousal aspect of acute hypoxemia, whereas we studied animals in a steady state.

Likewise, Matsumoto *et al.*[19] studied hepatic blood flow in awake and hypoxemic (FI_{O_2} 0.12) rats in the presence of subanesthetic concentrations of volatile anesthetics. Our value for total hepatic blood flow during awake normoxemia was less than theirs, and our values during anesthesia and hypoxemia were much less than theirs. Again, however, it must be emphasized that their model (1.5 h of hypoxemia with subanesthetic concentrations of volatile anesthetic) differs from ours. Also, the MAP of their animals during hypoxemic anesthesia was much greater than ours, perhaps reflecting the subanesthetic state.

The only difference in response to hypoxemia among the anesthetics that we studied occurred in the cerebral circulation. Animals anesthetized with isoflurane had a significantly greater cerebral blood flow during hypoxemic anesthesia than did those anesthetized with enflurane. This was the result of a significant difference in cerebral vascular resistance between the two anesthetics.

In summary, we determined the effects of normocapnic hypoxemia on regional blood flows in awake animals and in those anesthetized with one of three volatile anesthetics. We found that 1) during hypoxemia, anesthesia either decreased blood flow or abolished the compensatory increases in flow to vital organs that occurred in awake animals, and 2) among the anesthetics, the responses to hypoxemia were similar except in the cerebral circulation, where blood flow during hypoxemia was greater in animals anesthetized with isoflurane as compared with those receiving enflurane.

The authors gratefully acknowledge the expert technical assistance of Ms. M. Susan Walker, B.S.

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