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Hepatic Oxygen Supply during Halothane or Isoflurane Anesthesia in Guinea Pigs

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The present study was designed to determine changes in hepatic oxygen supply in guinea pigs during halothane or isoflurane anesthesia. Twenty-seven guinea pigs were randomly divided into three equal groups: control (no anesthesia) group, and animals anesthetized with halothane or isoflurane to decrease mean arterial pressure (MAP) by 50%. Hepatic arterial blood flow (HABF) and portal blood flow (PBF), as well as arterial and portal venous blood oxygen content, were determined in awake animals (stage I, baseline values), and during anesthesia (stage II). HABF was found to be extremely low (0.04 ml · min^{-1} · g^{-1}) during both stages of observation in the control (no anesthesia) group, as well as during stage I (awake) in animals treated with halothane or isoflurane. Equal degrees of arterial hypotension during halothane and isoflurane anesthesia were accompanied by decreased HABF during halothane (37%), but no significant change in HABF during isoflurane anesthesia. PBF decreased significantly in both experimental groups; however, the decrease was more prominent during halothane than during isoflurane anesthesia (57% *vs.* 23%). The observed hepatic circulatory changes led to a 65% decrease in hepatic oxygen delivery during halothane, but only a 34% decrease during isoflurane anesthesia. The present study does not exclude the possibility that liver damage in the guinea pig model is related to the reductive metabolism of halothane or any other mechanism. However, the extremely low HABF and a prominent reduction in both HABF and PBF during halothane anesthesia may be responsible for hepatic damage observed in the guinea pig model. (Key words: Guinea pigs. Anesthetics, volatile: halothane; isoflurane. Liver: blood flow; oxygen supply.)

THERE ARE NUMEROUS reports of hepatic injury developing after halothane anesthesia.[1,2] Experimentally, liver injury by halothane can be induced in several animal models. The most widely used is the rat model which demonstrated halothane-related hepatotoxicity in rats pretreated with phenobarbital (to produce enzyme induction) and then anesthetized with halothane in hypoxic conditions.[3,4] It is proposed that certain intermediate products, accumulated during the reductive metabolism of halothane, which takes place during hypoxia, could be responsible for the hepatic injury.[3,5,6] It is also suggested that hypoxia *per se* produces liver injury without direct involvement of the metabolic products of halothane.[7] However, the rat model by itself presents some problems: the reproducibility of hepatic injury depends on enzyme induction, sex, species, age, temperature, and season variations.[3-5] This model does not seem to be very helpful in elucidating certain types of postoperative liver dysfunction seen in humans.[8] Although the experimental models have given some valuable information regarding halothane-induced hepatotoxicity, they have not clarified the etiology and pathogenesis of this process in humans.[1,9]

A model using guinea pigs to produce and study halothane-induced hepatic injury was introduced more than a decade ago.[10] This model was challenged because of the severe hypotension caused by halothane.[11,12] However, the model has been recently modified and used again to study halothane hepatotoxicity.[13] In more recent experiments, hepatic necrosis was observed in non-pretreated, non-hypoxic guinea pigs after halothane, but not after isoflurane anesthesia.[13] Although the authors suggest that the liver injury was due to halothane biotransformation, the data do not show that the liver injury was associated with an increase in metabolites from halothane degradation. The investigators also speculated that the hepatic oxygen supply was similar in their two groups (halothane and isoflurane) since similar values of mean arterial pressure (MAP) and blood gases were maintained.[13] Data obtained from other animal models show that, during equipotent doses of halothane or isoflurane, accompanied by similar decreases in blood pressure, different decreases in hepatic blood flow and oxygen supply occurred; specifically, isoflurane facilitated a much better hepatic oxygen supply than halothane.[14-16] Therefore, the assumption that similar decreases in MAP during halothane and isoflurane anesthesia in guinea pigs were accompanied by a similar decrease in hepatic blood flow could be in error.

This study was designed to test the hypothesis that similar changes in MAP and oxygen content in arterial blood during halothane or isoflurane anesthesia in guinea pigs are accompanied by similar changes in hepatic oxygen supply. If the hypothesis is confirmed, the speculations that the differences in hepatotoxicity between halothane-or isoflurane-treated guinea pigs are related to metabolic biotransformation of halothane would be indirectly supported. On the other hand, if the hypothesis is rejected, and the halothane-treated animals develop a more severe hepatic oxygen deprivation than isoflurane-treated animals, then the data ob-

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served by Lunam *et al.*[13] may have an alternative explanation: hepatic oxygen deprivation *per se*, without the direct involvement of halothane metabolism, could be responsible for halothane-induced hepatic damage.

Methods and Materials

This study was performed on 27 adult male Charles River guinea pigs weighing 500–550 grams. They were fed rabbit pellets and given water with added ascorbic acid. Anesthesia was induced with isoflurane in oxygen in a chamber. Surgical preparation of the animals was also performed with isoflurane administered *via* mask. The animals were fixed to a surgical table over a heated electrical blanket, maintaining body temperature at 37° C. The left ventricle was cannulated *via* the left carotid artery and the distal aorta was catheterized *via* the femoral artery with a polyethylene tubing of an appropriate size. A laparotomy was performed and a 20-gauge catheter was placed into the portal vein. All incisions were closed. The catheters were externalized and fixed. Blood pressure was continuously monitored using a transducer and a Grass® polygraph.

In approximately 60–90 min after surgical preparation, when the animals were awake, responsive to sounds, and able to move freely in the cage, arterial and portal venous blood (0.4 ml of blood from each vessel) was obtained for measurements of *p*H, blood gas tensions, and oxygen content using an Instrumentation Laboratory (IL) 813 *p*H Gas Analyzer and IL 282 Co-oximeter, respectively. The hemoglobin of the guinea pig and the human has a relatively high level of 2,3-diphosphoglycerate and, therefore, a high affinity for oxygen; P_{50} values range from 26.9–27.8 mmHg.[17–19] A set of 15 μm spheres labeled ^{95}Nb or ^{113}Sn in 1 ml of saline (approximately 150,000–200,000 spheres suspended in 10% dextran solution and Tween 80) was injected into the left ventricle (baseline values at awake state, stage I).

The microsphere technique used in these experiments has already been described.[14,15,20] All microspheres were obtained from the 3M Co., St. Paul, Minnesota, and were checked for size, aggregation and fragmentation. Microspheres were mixed with normal saline in a 1 ml syringe and shaken vigorously on a Vortex mixer for 2 min before injection. Blood reference samples were withdrawn by a Holter Precision roller pump from the distal aorta at a rate of 1 ml $\cdot$ min^{-1} for 2.5 min and collected in five test tubes.

The animals were divided into three groups: control (no anesthesia), halothane, and isoflurane, with nine animals per group. Each animal was randomly assigned to different treatment groups using a table of random numbers. The control group was exposed to 40% oxygen in nitrogen without endotracheal intubation for 1 h. Halothane or isoflurane was administered in 40% oxygen in nitrogen *via* an endotracheal tube, also for 1 h. Controlled ventilation with a constant Pa_{CO_2} was assured. The anesthetics (halothane or isoflurane) were administered until MAP was stabilized at 50% of baseline values for at least 45 min. Inspired concentrations of the anesthetics were measured using an Engstrom EMMA anesthetic analyzer. A second set of 15 microspheres labeled differently, ^{113}Sn or ^{95}Nb, was injected using the same technique as was used for the first microspheres injection (stage II).

After the experiments were completed, the animals were killed by an intracardiac injection of KCl. The position of the catheter in the left ventricle was verified. All splanchnic organs were removed for activity counting and blood flow determinations. Activity found in the liver was used to calculate hepatic arterial blood flow (HABF), while activity found in all other splanchnic organs (stomach, intestines, pancreas, spleen, and mesentery) was used to calculate portal blood flow (PBF). Radioactivity in the tissues and reference blood samples was analyzed with a Tracor 2250 Gamma Counting System. This method employs an isotope calibration file that contains the decay rate, the number of counts per microsphere, and the spectral definition of the isotopes used in the study. Once loaded into memory, this calibration file is used by the Microspheres Analysis (MSA) program to compare the spectra contained in the file with the spectra of the blood or tissue sample. The MSA calculates cardiac output and blood flow per gram of tissue. If the difference between the values of blood flow in the kidneys was greater than 10%, and/or if the number of spheres in any tissue sample was less than 400, the observed results were discarded since this indicated an inadequate mixing of microspheres in the blood stream.

Hepatic oxygen delivery was calculated as follows:

$$HDO_2 = CaO_2 \cdot HABF + CpvO_2 \cdot PBF,$$

where HDO_2 is hepatic oxygen delivery in ml $O_2 \cdot min^{-1} \cdot g^{-1}$; CaO_2 and $CpvO_2$ are arterial and portal venous oxygen content, respectively, in ml $O_2 \cdot ml^{-1}$ of blood; and HABF and PBF are hepatic arterial blood flow and portal venous blood flow, respectively, in $ml \cdot min^{-1} \cdot g^{-1}$ of the liver.

Data were summarized as the standard error of the mean for each group (control, halothane, and isoflurane) and both stages. The variables were also expressed as percent of baseline values. Comparison of groups at each stage utilized a one-way analysis of variance. Tests of significance for percent changes used a one-sample *t* test. Multiple comparisons between pairs of group means used the Fisher's protected least signifi-

cant difference test. Pearson correlation coefficients were used to measure the association between pairs of measurements.[21] Differences were declared significant with $P < 0.05$.

Results

Baseline (awake) values characterizing main cardiovascular function and hepatic oxygen supply (stage I) did not differ significantly among the groups in any of the variables studied (table 1). Values in the control (no anesthesia) group at stage II were no different from those during stage I. Values of arterial *p*H, P_{CO_2}, and oxygen content were similar in all three groups of animals during both stages of experiments (tables 1, 2). These results demonstrate that the model used in this study did not deteriorate with time, and the changes observed resulted only from the anesthetic in question. According to experimental design, MAP in the halothane and isoflurane groups decreased during stage II to a similar extent: during halothane anesthesia (0.95 ± 0.11 vol%), MAP decreased from 79 ± 2.4 to 42 ± 0.9 mmHg; during isoflurane anesthesia (1.22 ± 0.17 vol%), MAP decreased from 84 ± 3.1 to 43 ± 1.7 mmHg (fig. 1). However, at the same time, cardiac output (CO) decreased twice as much during halothane as during isoflurane anesthesia. Variables characterizing hepatic circulation and oxygen supply show a striking difference between the two experimental groups: the values of HABF, total hepatic blood flow (THBF), and hepatic oxygen delivery (HDO_2) were significantly less in animals treated with halothane than in animals anesthetized with isoflurane (fig. 1, table 2).

Discussion

The purpose of this study was to test the hypothesis that similar decreases in MAP during halothane and isoflurane anesthesia are accompanied by equal changes in oxygen delivery to the liver in the guinea pig model. The study rejects the hypothesis. Halothane anesthesia accompanied by a 50% decrease in MAP was associated with a much greater decrease in hepatic oxygen supply compared with isoflurane, which was also administered at concentrations sufficient to decrease blood pressure 50%. Blood sampling resulted in a loss of approximately 3.3 ml of blood before the last injection of microspheres. An additional 2.5 ml of blood was withdrawn at the time of the second set of microspheres injection, which was during the last 2.5 min of the experiments. Such blood loss represents approximately 10–12% of total blood volume of the guinea pig.[22] This blood loss probably did not play a significant role in either the overall results or the conclusions of this study, since all animals in the three groups experienced equal blood loss and, thus, the differences among the groups resulted apparently from the anesthetics rather than blood loss. Approximately similar blood loss took place in the study by Lunam *et al.*;[13] therefore, it is not surprising that the concentrations of the anesthetics required to achieve a 50% decrease in MAP were very similar in the present study (mean values of 0.95% halothane and 1.22% isoflurane), and in the study by Lunam *et al.* (mean values of 0.95% halothane and 1.11% isoflurane[13]). Thus, we purposely used experi-

TABLE 1. Baseline (Awake) Values for Control (No Anesthesia), Halothane and Isoflurane Groups (Mean ± SE)

Variable	No Anesthesia	Halothane	Isoflurane
*p*H	7.45 ± 0.01	7.43 ± 0.01	7.41 ± 0.01
Pa_{CO_2}	23.6 ± 0.77	26.4 ± 1.2	26.9 ± 1.1
MAP	79 ± 2.6	79 ± 2.4	85 ± 3.1
CO	171 ± 14.5	207 ± 35.9	169 ± 20.4
HABF	0.04 ± 0.008	0.04 ± 0.010	0.04 ± 0.006
PBF	2.11 ± 0.25	2.06 ± 0.13	1.97 ± 0.24
THBF	2.15 ± 0.25	2.10 ± 0.13	2.00 ± 0.24
SaO_2	98.6 ± 0.35	98.1 ± 0.31	97.9 ± 0.33
$SpvO_2$	88.8 ± 1.21	88.4 ± 2.34	89.3 ± 2.27
CaO_2	18.2 ± 0.12	18.1 ± 0.15	18.2 ± 0.30
$CpvO_2$	16.3 ± 0.23	16.2 ± 0.50	16.5 ± 0.26
$HADO_2$	0.007 ± 0.001	0.007 ± 0.001	0.007 ± 0.001
$PVDO_2$	0.34 ± 0.04	0.33 ± 0.01	0.32 ± 0.03
HDO_2	0.35 ± 0.04	0.34 ± 0.01	0.33 ± 0.03

Pa_{CO_2} = arterial carbon dioxide tension (mmHg); MAP = mean arterial pressure (mmHg); CO = cardiac output ($ml \cdot min^{-1}$); HABF, PBF, THBF = hepatic arterial blood flow, portal blood flow, total hepatic blood flow, respectively ($ml \cdot min^{-1} \cdot g^{-1}$); SaO_2, $SpvO_2$ = oxygen saturation in arterial and portal venous blood, respectively (%HbO_2); CaO_2, $CpvO_2$ = oxygen content in arterial and portal venous blood, respectively ($ml\ O_2 \cdot dl^{-1}$); $HADO_2$, $PVDO_2$, HDO_2 = hepatic oxygen delivery *via* hepatic artery, portal vein, and total hepatic oxygen delivery, respectively ($ml\ O_2 \cdot min^{-1} \cdot g^{-1}$). There were no significant differences among groups for any value (n = 9 for each group).

TABLE 2. Percent of Baseline (Awake) Values for Control (No Anesthesia), Halothane and Isoflurane Groups (Mean ± SE)

Variable	No Anesthesia	Halothane	Isoflurane
MAP	94.4 ± 2.06	53.4 ± 2.31*	51.3 ± 2.09*
CO	91.1 ± 3.81	48.4 ± 6.59*	78.3 ± 5.90*†
HABF	109.5 ± 21.16	63.0 ± 4.28*	93.8 ± 5.74†
PBF	94.2 ± 2.51	42.8 ± 4.00*	77.3 ± 2.48*†
THBF	94.2 ± 2.50	43.1 ± 3.93*	77.6 ± 2.42*†
SaO_2	99.9 ± 0.12	99.8 ± 0.09	100.0 ± 0.26
$SpvO_2$	92.2 ± 2.77	82.8 ± 2.12*	85.9 ± 3.83
CaO_2	98.5 ± 0.72	98.4 ± 0.64	98.4 ± 1.80
$CpvO_2$	96.4 ± 2.50	81.5 ± 2.33*	84.4 ± 4.09
$HADO_2$	108.3 ± 21.48	61.9 ± 4.05*	92.4 ± 6.18†
$PVDO_2$	90.7 ± 2.73	34.6 ± 3.06*	65.1 ± 3.49*†
HDO_2	90.7 ± 2.71	35.1 ± 3.01*	65.8 ± 3.45*†

See footnote to table 1 for abbreviations. All values are expressed in percent of control.

* $P < 0.05$ *versus* control.

† $P < 0.05$ *versus* halothane.

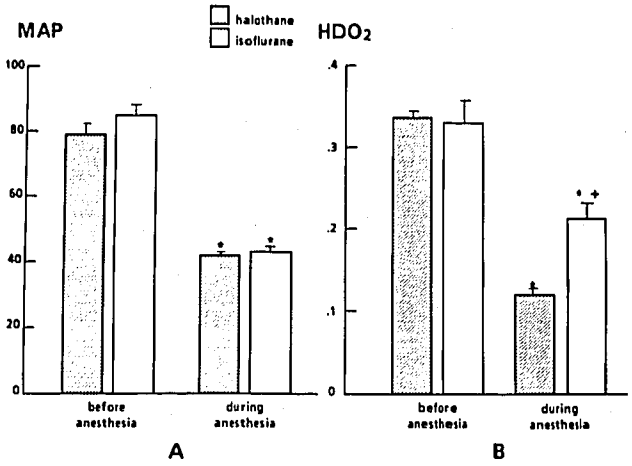

FIG. 1. Changes in mean arterial pressure (*A*. MAP in mmHg) and hepatic oxygen delivery (*B*. HDO_2 in ml $O_2 \cdot min^{-1} \cdot g^{-1}$) in guinea pigs during halothane and isoflurane anesthesia. $^*P < 0.05$ compared with values observed before anesthesia. $^+P < 0.05$ compared with values observed during halothane anesthesia.

mental conditions (degree of arterial hypotension, blood loss due to sampling, and dose of anesthetics required) identical to those used in the study by Lunam *et al.*, who demonstrated that anesthesia with halothane and isoflurane producing similar degrees (50%) of arterial hypotension resulted in different effects on the liver: namely, halothane led to clear hepatic damage, while isoflurane did not.[13] Lunam *et al.* speculate that the hepatic damage observed in guinea pigs treated with halothane, but not with isoflurane, resulted from halothane metabolism, since similar degrees of arterial hypotension and similar changes in arterial blood gases probably meant similar hepatic oxygen supply.[13] The present study clearly demonstrates that such speculation is not justified.

It has been demonstrated, in other species (dogs, pigs, rats), that halothane and isoflurane administered in equipotent doses according to MAC and/or according to a degree of arterial hypotension are accompanied by different degrees of splanchnic circulatory disturbances, resulting in different reductions in hepatic oxygen supply. For example, in dogs, equipotent doses of halothane or isoflurane, accompanied by approximately similar decreases in MAP and even CO, were associated with very different types of hepatic circulatory disturbances; isoflurane increased HABF, while halothane maintained HABF in small doses and decreased HABF in larger doses.[14] Obviously, such changes in hepatic circulation were accompanied by a much more prominent decrease in hepatic oxygen supply during halothane compared with isoflurane anesthesia. In phenobarbital pretreated hypoxic rats, equipotent doses of halothane and isoflurane were also accompanied by different reductions in hepatic blood flow and in hepatic oxygen supply: HABF, THBF, and HDO_2 decreased twice as much during halothane anesthesia compared with equipotent doses of isoflurane.[15] Ross *et al.* observed similar changes in mean values of HABF; however, the difference between values did not reach a statistically significant level.[4] In intact rats, the values of PBF and HABF were also much lower during halothane compared with isoflurane.[16] In miniature pigs, hepatic oxygen supply during halothane anesthesia was approximately 0.6–0.7 of that observed during isoflurane anesthesia when administered in conditions of similar surgical stress (Gelman *et al.*, unpublished data). Thus, in this regard, the guinea pigs do not seem to be very different from other studied species.

On the other hand, with regard to the hepatic circulation, guinea pigs appear to be very different from other species. We observed extremely low HABF in these animals in all three groups before halothane or isoflurane was administered. The arterial fraction of THBF in our observations equaled approximately 2% of THBF (table 1). We do not doubt the accuracy of the HABF measurements, since the number of microspheres in all liver samples from 27 animals included in the analysis exceeded 500. Four guinea pigs (besides the 27 animals presented in this study) with less than 400 spheres in liver samples also had a difference greater than 10% between the values of blood flow in the right and left kidneys. Therefore, according to experimental design, these animals were excluded from the study. In addition, similar values of HABF in guinea pigs were observed by other investigators.[23,24]

The low values of HABF and the low arterial fraction of total hepatic blood supply in guinea pigs are very different from the majority of other species, where HABF represents approximately 20–35% of THBF.[25,26] Such a difference might make guinea pig livers extremely susceptible to ischemic insult. In dogs, for example, calculations show that, if HABF is 20% of THBF, the hepatic arterial blood contributes 27% of hepatic oxygen uptake; if HABF is 30%, the arterial blood contributes 65% of the oxygen consumed.[26] It seems conceivable, therefore, that the extremely low ratio of HABF to PBF in guinea pigs can play an important role in the susceptibility of the liver of the guinea pig to ischemic/hypoxic insult. This can be one reason guinea pigs develop hepatic damage during halothane anesthesia without additional hypoxia and/or phenobarbital pretreatment. The peculiar hepatic blood and oxygen supply in guinea pigs probably results in a relatively narrow margin of safety for the liver, or, in other words, in a relatively small difference between normal

hepatic oxygen supply and inadequate hepatic oxygen supply, which may easily develop during certain conditions, *e.g.*, hypoxia, hypotension, low cardiac output, etc. This may suggest that the guinea pig model is suitable for studying some ischemic mechanisms of liver injury, since hepatic ischemic injury would develop before cerebral or cardiac death; however, the model does not seem to be appropriate for studying hepatic circulatory responses to anesthetics or any other insult.

The role of HABF in hepatic oxygen supply has been appreciated for years.[26] Some studies have even suggested that the hepatic oxygen requirement itself governs the reciprocity between PBF (with partially deoxygenated blood) and HABF.[27,28] It has been suggested the the loss of the PBF-HABF reciprocal relationship during anesthesia may be responsible for the development of postoperative hepatic dysfunction.[29]

The sensitivity of guinea pigs to halothane appears to be genetically determined.[30] These observations can be explained not only by the metabolic or immunologic theories of an induced hepatic injury, but also by the hypoxic hypothesis: some guinea pigs might have a higher hepatic oxygen demand and/or might develop a severer reduction in hepatic oxygen supply due to a particular sensitivity of the arterial hepatic vasculature to halothane than other animals, resulting in a lower oxygen supply-demand ratio.

The possibility that the two anesthetics studied affect hepatic oxygen demand differently should be considered, since, if, for example, halothane decreased hepatic oxygen demand to a much greater extent than isoflurane, the hepatic oxygen supply-demand ratio could have been similar for the two anesthetics in question. Hepatic oxygen demand and/or uptake during halothane or isoflurane anesthesia are very similar in dogs[31] and in rats.[32] Therefore, if these two anesthetics affect oxygen demand in guinea pig livers, as they do in dogs and rats, the speculation that halothane may induce liver damage by ischemic mechanisms would be justified. However, hepatic oxygen uptake was not determined in this study, and, therefore, the possibility that the difference in the hepatic oxygen supply-demand ratio between the halothane and isoflurane groups was less dramatic than the observed difference in hepatic oxygen supply, cannot be ruled out completely.

In summary, the results of this study reject the hypothesis that maintained arterial oxygen content and similar reductions in MAP induced by halothane or isoflurane are accompanied by similar reductions in hepatic oxygen supply. The results demonstrate that halothane produces more severe hepatic oxygen deprivation than isoflurane when administered in doses accompanied by similar decreases in MAP. The present study does not exclude the possibility that liver damage in the guinea pig model is related to the reductive metabolism of halothane (which takes place in hypoxic conditions) or any other mechanism. However, the absence of association between hepatic injury and metabolites produced during the reductive biotransformation of halothane[13] does not fit the hypothesis that halothane metabolism is directly responsible for halothane-induced liver damage. On the other hand, the extremely low HABF in guinea pigs, in conjunction with the halothane-induced severe reduction in hepatic oxygen supply, makes it conceivable that the hepatic damage observed in the guinea pig model during halothane anesthesia[13,30] is related to hepatic oxygen deprivation *per se* without a direct involvement of halothane metabolism.

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