

# Hepatic Oxygen Supply-Uptake Relationship and Metabolism during Anesthesia in Miniature Pigs

Kouichi Nagano, M.D.,\* Simon Gelman, M.D., Ph.D.,† Dale A. Parks, Ph.D.,‡ Edwin L. Bradley, Jr., Ph.D.§

The study evaluated the effects of different anesthetics on the hepatic oxygen supply-demand relationship and hepatic lactate uptake (HLu). Miniature pigs ( $n = 33$ ), weighing 20–31 kg, were divided into five groups and accordingly anesthetized with halothane, isoflurane, enflurane (0.9%, 1.5%, and 2.2% end-expired concentrations, respectively), fentanyl (100  $\mu\text{g}/\text{kg}$  iv bolus followed by a continuous infusion of 50  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ), or sodium pentobarbital (30 mg/kg iv bolus followed by a continuous infusion at a rate of 1–2 mg  $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). The surgical preparation allowed the authors to induce a stepwise decrease in hepatic blood supply without congestion in the preportal tissues. Prior to induced hepatic hypoperfusion, the values of hepatic oxygen delivery ( $\text{HDO}_2$ ) were the greatest in the isoflurane and fentanyl groups and the smallest in the halothane group, while the values of hepatic oxygen uptake ( $\text{HVO}_2$ ) were the smallest in the halothane group without differences among the other four groups. During stepwise decrease in hepatic blood and oxygen supply, HLu started to decrease at higher values of hepatic oxygen delivery in the fentanyl group ( $\text{HDO}_2 = 10 \text{ mlO}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ) than in all others ( $\text{HDO}_2 = 6\text{--}7 \text{ mlO}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ). At values of  $\text{HDO}_2$  equal to 2–3  $\text{mlO}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ , the values of HLu became negative, signifying that the liver began to release rather than to metabolize lactate. There was a linear relationship between the values of  $\text{HDO}_2$  and hepatic venous oxygen tension or saturation ( $r = 0.96$ ;  $P < 0.001$ ). Among the five anesthetics studied, isoflurane and fentanyl provided the greatest values of  $\text{HDO}_2$  and hepatic venous oxygen supply-demand ratios. Halothane decreased hepatic oxygen demand and could have provided some protection from hepatic oxygen deprivation. However, the decrease in hepatic oxygen delivery produced by halothane was greater than the decrease in hepatic oxygen demand; therefore, halothane might not be the anesthetic of choice for surgical procedures where hepatic hypoxia is anticipated. Oxygen saturation in hepatic venous blood is an indicator of adequacy of hepatic oxygen supply. (Key words: Anesthetics, intravenous: fentanyl; pentobarbital. Anesthetics, volatile: enflurane; halothane; isoflurane. Hypoxia. Liver: blood flow; function; metabolism; oxygen consumption.)

DIFFERENT ANESTHETICS decrease hepatic blood flow to different degrees, thereby decreasing hepatic oxygen supply to a varying extent.<sup>1,2</sup> Surgical stress, particularly laparotomy, is associated with a significant decrease in hepatic blood and oxygen supply.<sup>1,3,4</sup> In addition, many surgical procedures are accompanied by a temporary interruption or decrease in hepatic blood supply. Such pro-

cedures include surgery on the thoracic aorta, hepatic trauma, liver resection, and particularly, liver transplantation. On the other hand, some anesthetics may provide a certain degree of protection from an ischemic insult in some tissues. For example, barbiturates and isoflurane at clinically relevant doses may protect the brain from an ischemic insult by decreasing cerebral oxygen demand.<sup>5</sup> Isoflurane may also enhance recovery of the myocardium in the postischemic state.<sup>6</sup> It is conceivable that different anesthetics can affect hepatic oxygen demand by several mechanisms. Anesthetics can decrease hepatic metabolic rate and oxygen requirements: some experiments on isolated perfused livers demonstrated a decreased hepatic oxygen uptake in conditions of constant hepatic blood flow and oxygen supply.<sup>7–9</sup> Anesthetics may provide a certain protection to the liver by reducing hepatic oxygen demand. It seems desirable to identify an anesthetic that provides the optimal relationship between hepatic oxygen supply and demand.

The main hypothesis of the present study can be formulated as follows: anesthetics affect the hepatic oxygen supply-demand relationship differently with some anesthetics providing a greater margin of safety and protection against ischemic injury. The main objective of this study is to evaluate the effects of commonly used anesthetics on hepatic oxygen supply-demand relationship and hepatic lactate uptake, and to identify the anesthetic that provides the most favorable effects.

## Materials and Methods

These studies received approval from the University of Alabama Animal Use Committee. Thirty-three female miniature pigs (Hanford strain from Charles River Laboratories, Wilmington, MA), weighing 20–31 kg, fasted for 24 h before the experiment. The pigs were anesthetized with sodium methohexital 20 mg/kg im and paralyzed with pancuronium bromide 0.1 mg/kg iv. Additional doses of pancuronium (30–50% of the first dose) were administered every 30–40 min to prevent any movement. Controlled ventilation with nitrous oxide (60%) in oxygen using an Air-Shield® ventilator (Air-Shield Inc, Narco Health Co, Hatboro, PA) was provided to keep  $\text{PaCO}_2$  at 35–40 mmHg. Body temperature was monitored by a thermistor probe placed in the rectum and maintained at 38°C throughout the experiment using heating pads. Lactated Ringer's solution was infused at a rate of 5 ml  $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  throughout the experiment. The

\* Research Fellow.

† Professor and Chairman.

‡ Assistant Professor of Anesthesiology, Physiology, and Biophysics.

§ Professor of Biostatistic and Biomathematics.

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Address reprint requests to Dr. Gelman.

pigs were randomly divided into five groups. Three volatile anesthetics were administered to maintain end-expired concentrations of the anesthetics at 0.9%, 1.5%, and 2.2% for halothane ( $n = 7$ ), isoflurane ( $n = 6$ ), or enflurane ( $n = 7$ ), respectively. End-expired concentrations of the volatile anesthetics were monitored with a Puritan-Bennett anesthetic agent monitor calibrated every day before the experiments. The animals of the fentanyl group ( $n = 6$ ) received fentanyl  $100 \mu\text{g}/\text{kg}$  iv bolus followed by a continuous infusion of  $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . The concentration of plasma fentanyl was measured before and after hepatic ischemia by radioimmunoassay.<sup>10</sup> The arterial plasma fentanyl concentrations (mean  $\pm$  SD) before and after hepatic ischemia were  $30.1 \pm 9.9 \text{ ng/ml}$  and  $45 \pm 11.6 \text{ ng/ml}$ , respectively. The animals of the pentobarbital group ( $n = 7$ ) received sodium pentobarbital,  $30 \text{ mg}/\text{kg}$  iv bolus followed by a continuous infusion at a rate of  $1\text{--}2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . At the end of surgical preparation nitrous oxide was discontinued and end-expired concentrations of the volatile anesthetics or the infusion rates of fentanyl and pentobarbital were not changed.

#### SURGICAL PREPARATION

Surgical preparation was performed under anesthesia with one of the five anesthetics mentioned above. Both carotid arteries and jugular veins were exposed and isolated. One carotid artery was cannulated for blood sampling and recording of blood pressure. The remaining carotid artery was used for blood supply to the hepatic artery. The left jugular vein was cannulated for drug administration and infusion of fluid. Laparotomy was performed, the common hepatic artery isolated, and the left gastric artery and the gastroduodenal arteries ligated. The portal vein was also exposed and the gastroduodenal vein was ligated. Both the portal vein and hepatic artery were transected carefully so that the plexuses innervating the liver remained intact. Heparin was administered iv in a dose of  $300 \text{ U}/\text{kg}$  followed by additional heparin injections of  $100 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Hepatic arterial and portal venous blood flows were measured with an electromagnetic flowmeter (700 Series Cliniflow II, Carolina Medical Medical Electronics, Inc., King, NC) using cannulating probes. The probes were factory calibrated. The accuracy of the measurements were verified by passing blood or saline at different rates through the probes between the experiments. The rates were then compared with the flowmeter output; the differences did not exceed 5%.

A carotid artery and the common hepatic artery were transected and the proximal end of the carotid artery connected to the hepatic end of the hepatic artery by a polyethylene tubing with a cannulating electromagnetic flow probe of appropriate size (10 mm circumference).

The distal end of the carotid artery and the proximal end of the hepatic artery were ligated. The portal vein was also transected and a polyethylene tubing with a cannulating electromagnetic flow probe of appropriate size (25 mm circumference) was inserted between both ends of the portal vein. Preliminary experiments demonstrated that the pressure gradient across the tubing with the electromagnetic flowmeter in the portal vein did not exceed 2 mmHg. This tubing contained a Y connector that connected the portal vein with the right jugular vein in such a way that portal blood could flow either to the liver through the electromagnetic probe and hepatic end of the portal vein or to the jugular vein and systemic circulation (fig. 1). The tubings with the two electromagnetic probes (measuring hepatic arterial and portal venous blood flows) were connected to pressure transducers (COBE, Lakewood, CO;  $350 \Omega$ , sensitivity of  $5 \text{ uV}/\text{V}/\text{mmHg}$ ) for continuous monitoring and recording of portal and hepatic arterial pressures. The hepatic vein in the median lobe was cannulated subdiaphragmatically through the inferior (posterior) caval vein with a balloon-tipped catheter for blood sampling and pressure monitoring. The catheter was advanced into the hepatic vein until occlusion and then withdrawn 3 cm to ensure free positioning of the catheter tip in the hepatic vein. The balloon was slightly inflated and blood samples were withdrawn slowly to ensure that blood from the caval vein did

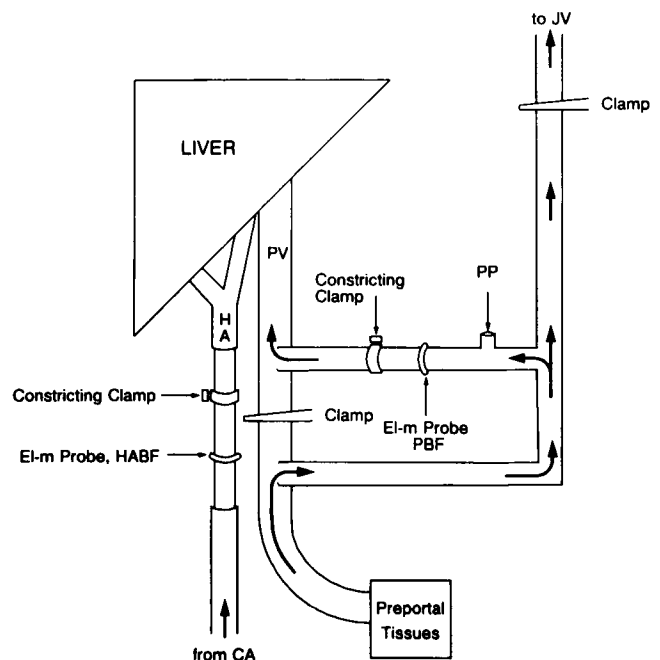


FIG. 1. The schematic representation of the experimental preparation. HA = hepatic artery; PV = portal vein; CA = carotid artery; JV = jugular vein; EL-m = electromagnetic; HABF = hepatic arterial blood flow; PBF = portal blood flow; PP = portal pressure.

not mingle with the hepatic venous blood. The position of the catheter was verified after each experiment.

#### EXPERIMENTAL PROTOCOL

The hemodynamic status of the animals was allowed to stabilize for 30 min, after which baseline measurements and blood samples were obtained. The observations were made during five stages. At stage 1 (baseline), flows through the hepatic artery and portal vein were not restricted while the tubing connecting the portal vein with the jugular vein was occluded. At stages 2–5, the hepatic artery was completely occluded ( $HABF = 0$ ). At stage 2, the tubing connecting the portal vein with the jugular vein was occluded, thereby portal blood flow to the liver was fully preserved. At stages 3–5, portal blood flow was gradually decreased to 75%, 50%, and 25%, respectively, of the values observed at stage 1. This was achieved by an unclamping of the tubing connecting the portal vein with the jugular vein and by a gradual constricting of the tubing connecting the transected ends of the portal vein. At each stage, 15 minutes were allowed for stabilization before the measurements and blood samples were obtained. Experiments with hemoglobin concentrations lower than 10 g/dl at any stage of observation were excluded from the study and not reported.

#### MEASUREMENTS AND CALCULATIONS

Systolic, diastolic, and mean arterial pressures (MAP), portal venous, and hepatic venous pressures were continuously recorded on a Grass® polygraph. Samples of arterial, portal, and hepatic venous blood were periodically obtained for  $pH$ /gas tensions and oxygen content analyses that were performed using an Instrumentation Laboratory model 1301  $pH$ /blood gas analyzer and model 282 Co-oximeter. The  $P_{50}$  of freshly tonometered pig blood was 33 mmHg at  $pH$  7.4.

Whole blood lactate concentrations in samples from these three vessels were also determined spectrophotometrically using a modification of the method.<sup>11</sup> The enzymatic oxidation method that was used in this study employs lactate dehydrogenase (LDH) to oxidize lactic acid to pyruvic acid with a concomitant reduction of a molar equivalent of  $NAD^+$ . The latter is monitored at 340 nm. We used a two-point kinetic method that uses a 10-mg/dl lactic acid standard. Alanine aminotransferase was added to force the reaction to completion through removal of pyruvate from the reaction (pyruvate plus glutamate to alanine and  $\alpha$  ketoglutarate). Blood (1 ml) was collected in a heparinized syringe and immediately placed in ice-cold 0.6-M perchloric acid (2 ml). The sample was mixed thoroughly and let stand for an additional 5 min. The sample was then centrifuged for 10 min at  $1500 \times g$ . The supernatant was used for the assays. The required

reagents were purchased from Calbiochem-Behring Corporation and the samples were processed using a centrifugal analyzer (Flexigem, Electro-Nucleonics, Inc.) equipped with an autoloader. All samples were analyzed in duplicate. The within-run precision (all samples run at a time) of the autoloader was 1.6% and the run-to-run precision was 2.3% (samples run at different times). The overall coefficient of variation (replicates of control serum) for the assay was approximately 3%. The correlation of this method to spectrophotometer was 0.996.

Hepatic oxygen delivery ( $HDO_2$ ), hepatic oxygen uptake ( $H\dot{V}O_2$ ), hepatic lactate delivery (HLd), and hepatic lactate uptake (HLu) were calculated as follows:

$$HDO_2 = CaO_2 \times HABF + Cpvo_2 \times PBF \quad (\text{mlO}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1})$$

$$H\dot{V}O_2 = HDO_2 - Chvo_2 \times (HABF + PBF) \quad (\text{mlO}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1})$$

$$HLd = La \times HABF + Lpv \times PBF \quad (\text{mg} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1})$$

$$HLu = HLd - Lhv \times (HABF + PBF) \quad (\text{mg} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1})$$

where  $HABF$  and  $PBF$  are hepatic arterial blood flow and portal blood flow, respectively, in  $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ;  $CaO_2$ ,  $Cpvo_2$ , and  $Chvo_2$  are oxygen content in arterial, portal venous, and hepatic venous blood, respectively in ml/dl; and  $La$ ,  $Lpv$ , and  $Lhv$  are whole lactate concentrations in arterial, portal, and hepatic venous blood, respectively, in mg/dl. Hepatic oxygen extraction ( $H\dot{V}O_2/HDO_2 \times 100\%$ ) was also calculated.

#### STATISTICAL ANALYSIS

The data were summarized as the mean  $\pm$  SD for each group and stage. Comparisons among the groups used a one-way analysis of variance. Comparisons among the stages for each group were made by a repeated measures analysis of variance. Individual comparisons of a pair of means used Fisher's protected least significant difference test.

The relationship between hepatic lactate uptake and hepatic oxygen uptake or delivery were estimated by linear least squares regression and the zero crossing points (the values of hepatic oxygen uptake and delivery at which the livers started to release lactate) were determined for each pig. These values were then analyzed by one-way analysis of variance.<sup>12</sup>

The following approach for determining the value of critical hepatic oxygen delivery (the greatest value of hepatic oxygen delivery at which hepatic oxygen uptake decreases or, in other words, becomes delivery dependent) was applied. For each pig, a least squares line was fit to the points of the hepatic oxygen delivery *versus* uptake plot observed during stages 3, 4, and 5. The point of

intersection of this line with the plateau, obtained by averaging the initial points (stages 1 and 2), was determined. The point of intersection of these two lines was considered to be the value of critical oxygen delivery ( $Cr\ HDO_2$ ).<sup>13</sup> The values of hepatic oxygen uptake at which the livers stopped metabolizing and started releasing lactate were defined as critical hepatic oxygen uptake. These values are represented by the points of intersection of the  $H\dot{V}O_2$  versus  $H\dot{L}u$  regression line with the line identifying "O" hepatic lactate uptake on the plot of  $H\dot{V}O_2$  versus  $H\dot{L}u$ . Then the values of critical oxygen delivery and critical oxygen uptake were analyzed by a one-way analysis of variance and Fisher's protected least significant difference test. Differences were declared statistically significant if  $P < 0.05$ .

**Results**

**HEPATIC OXYGEN DELIVERY AND UPTAKE DURING ANESTHESIA WITH NONRESTRICTED HEPATIC BLOOD FLOW (STAGE 1, BASELINE VALUES)**

Variables characterizing hepatic oxygen delivery during the period of nonrestricted hepatic blood flow for each group are presented in table 1. There were no statistically significant differences in the values of hepatic arterial blood flow among the groups; however, the values of portal blood flow were different, the greatest being in the isoflurane and fentanyl groups and the lowest in the halothane group. These differences in blood flow resulted in significant differences in hepatic oxygen delivery that was the greatest in the isoflurane and fentanyl groups and the smallest in the halothane group (fig. 2). The values of hepatic oxygen uptake were the smallest in the animals anesthetized with halothane without differences among the other four groups. Oxygen content and saturation in hepatic venous blood was the greatest in the isoflurane and fentanyl groups and the lowest in the enflurane group.

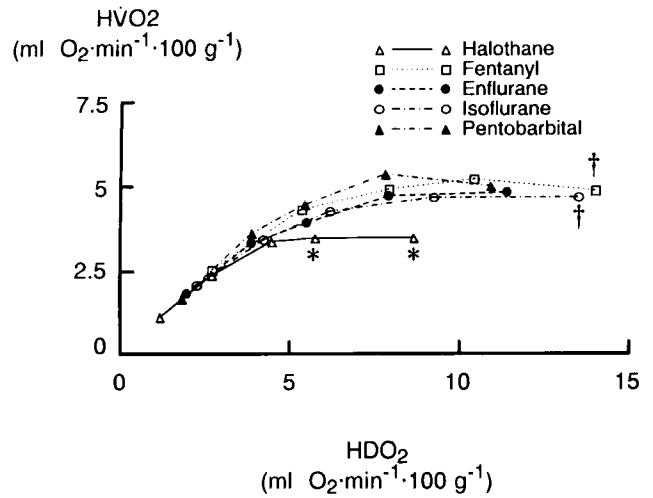


FIG. 2. Hepatic oxygen delivery ( $HDO_2$ ) relationship during stepwise decrease in hepatic oxygen delivery. \* $P < 0.05$  for the values of hepatic oxygen uptake during stages 1 and 2 versus four other anesthetics. † $P < 0.05$  for the values of hepatic oxygen delivery during stage 1 versus three other anesthetics.

However, these differences in hepatic oxygen delivery and uptake did not result in any noticeable differences in the hepatic lactate uptake.

**HEPATIC OXYGEN DELIVERY-UPTAKE RELATIONSHIP DURING STEPWISE DECREASE IN HEPATIC BLOOD AND OXYGEN SUPPLY (STAGES 1-5)**

Hepatic oxygen delivery-uptake relationship during stepwise decrease in blood flow was similar in all groups studied (fig. 2). Hepatic oxygen uptake ( $H\dot{V}O_2$ ) was independent of hepatic oxygen delivery ( $HDO_2$ ) and remained virtually unchanged (phase I) until  $HDO_2$  decreased to a certain point. During a further decrease in  $HDO_2$ ,  $H\dot{V}O_2$  became dependent on  $HDO_2$  (phase II); oxygen extraction was gradually increasing from 35-45%

TABLE 1. Hepatic Oxygen Delivery and Uptake During Nonrestricted Hepatic Blood and Oxygen Supply: Stage 1, Baseline Values, (Mean  $\pm$  SD)

Variables	Halothane	Isoflurane	Enflurane	Fentanyl	Pentobarbital
MAP	100 $\pm$ 10	112 $\pm$ 17	111 $\pm$ 18	139 $\pm$ 12*†‡§	126 $\pm$ 4
HABF	16 $\pm$ 7	23 $\pm$ 4	18 $\pm$ 13	17 $\pm$ 13	18 $\pm$ 8
PBF	49 $\pm$ 9†	84 $\pm$ 14*†‡§	64 $\pm$ 17†	80 $\pm$ 8*†‡§	65 $\pm$ 13†
$S_pVR$	1.47 $\pm$ 0.27	1.08 $\pm$ 0.26	1.24 $\pm$ 0.24	1.45 $\pm$ 0.27	1.43 $\pm$ 0.27
$HDO_2$	8.6 $\pm$ 2†	14.4 $\pm$ 0.8*†‡§	11.4 $\pm$ 3.3†	14.0 $\pm$ 3.5*†‡§	11.1 $\pm$ 2.8†
$H\dot{V}O_2$	3.4 $\pm$ 0.8*†‡§	5.0 $\pm$ 1*	5.9 $\pm$ 0.9*	4.9 $\pm$ 1.4*	5.1 $\pm$ 1*
$ShvO_2$	46 $\pm$ 11	58 $\pm$ 6‡	36 $\pm$ 18†	53 $\pm$ 13‡	43 $\pm$ 14
$H\dot{L}u$	4.4 $\pm$ 1.4	5.1 $\pm$ 3.1	4.7 $\pm$ 0.8	4.4 $\pm$ 1.6	4.8 $\pm$ 1.9

MAP = mean arterial pressure in mmHg, HABF and PBF = hepatic arterial and portal blood flows, respectively, in  $ml \cdot min^{-1} \cdot 100\ g^{-1}$ .  $S_pVR$  = splanchnic vascular resistance in  $mmHg \cdot min \cdot ml^{-1} \cdot 100\ g^{-1}$ .  $HDO_2$  and  $H\dot{V}O_2$  = hepatic oxygen delivery and hepatic oxygen uptake in  $mlO_2 \cdot min^{-1} \cdot 100\ g^{-1}$ .  $ShvO_2$  = oxygen saturation in hepatic venous

blood in percent.  $H\dot{L}u$  = hepatic lactate uptake in  $mg \cdot min^{-1} \cdot 100\ g^{-1}$ . \*  $P < 0.05$  versus halothane group. †  $P < 0.05$  versus isoflurane group. ‡  $P < 0.05$  versus enflurane group. §  $P < 0.05$  versus pentobarbital group.

TABLE 2. Hepatic Oxygen Delivery-Uptake Relationship Prior to and during Stepwise Decrease in Hepatic Blood and Oxygen Supply (Mean  $\pm$  SD)

Variables	Halothane	Isoflurane	Enflurane	Fentanyl	Pentobarbital
HDO <sub>2</sub> -HVO <sub>2</sub>	5.4 $\pm$ 1.6†	9.4 $\pm$ 1*‡	5 $\pm$ 3.6†	10.8 $\pm$ 3.8	5.9 $\pm$ 2.9
HDO <sub>2</sub> /HVO <sub>2</sub>	2.57 $\pm$ 0.30	3 $\pm$ 0.70‡	1.88 $\pm$ 0.59†	3.70 $\pm$ 1.63‡§	2.21 $\pm$ 0.59
crit HDO <sub>2</sub>	4.7 $\pm$ 0.7†	7.6 $\pm$ 1.4*	6.3 $\pm$ 2.2	6.6 $\pm$ 2.7	6.3 $\pm$ 1.2
HDO <sub>2</sub> -crit HDO <sub>2</sub>	4.1 $\pm$ 1.6	6.8 $\pm$ 1.1	4.4 $\pm$ 3.6	8.9 $\pm$ 4.6*	4.8 $\pm$ 2.1
Cr HDO <sub>2</sub> -HVO <sub>2</sub>	1.3 $\pm$ 0.6	2.6 $\pm$ 1	0.6 $\pm$ 1.8	1.8 $\pm$ 1.7	1.1 $\pm$ 0.7

HDO<sub>2</sub>-HVO<sub>2</sub> = hepatic oxygen delivery-uptake gradient observed during nonrestricted hepatic blood flow at stage 1 in mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>. HDO<sub>2</sub>/HVO<sub>2</sub> = hepatic oxygen delivery-uptake ratio observed during nonrestricted hepatic blood flow at stage 1 in mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>. crit HDO<sub>2</sub> = critical hepatic oxygen delivery, the greatest value of hepatic oxygen delivery at which hepatic oxygen uptake became oxygen delivery dependent (fig. 2). HDO<sub>2</sub>-crit HDO<sub>2</sub> = hepatic oxygen

delivery, critical hepatic oxygen delivery gradient in mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>. Cr HDO<sub>2</sub>-HVO<sub>2</sub> = critical hepatic oxygen delivery, uptake gradient in ml · min<sup>-1</sup> · 100 g<sup>-1</sup>.

\* *P* < 0.05 versus halothane group.

† *P* < 0.05 versus isoflurane group.

‡ *P* < 0.05 versus enflurane group.

§ *P* < 0.05 versus pentobarbital group.

at the first stage to 90–95% at the last stage of the experiment. This was associated with a gradual decrease in hepatic venous oxygen content and saturation. The values of hepatic oxygen uptake during the first two stages of experiments, when hepatic oxygen uptake was not yet oxygen delivery dependent, equaled approximately 3.5 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup> for halothane and was significantly greater (4.5–5 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>) in the remaining four groups without significant difference among them. The values of critical hepatic oxygen delivery, defined as the greatest value of HDO<sub>2</sub> at which HVO<sub>2</sub> became delivery dependent, were between 4.7 and 7.6 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g · liver<sup>-1</sup> (table 2). The only significant difference was observed between the isoflurane and halothane groups. The differences between hepatic oxygen delivery and critical hepatic oxygen delivery were largest in the isoflurane and fentanyl groups and lowest in the animals anesthetized with halothane and enflurane.

#### HEPATIC LACTATE UPTAKE DURING STEPWISE DECREASE IN HEPATIC BLOOD AND OXYGEN SUPPLY (STAGES 1–5)

There were no significant differences in blood lactate concentrations, hepatic lactate delivery, and hepatic lactate uptake at stage 1 (unrestricted hepatic blood flow) among the groups. Hepatic lactate uptake started to decrease earlier in the fentanyl group (at values of HDO<sub>2</sub> equal 10 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>) than in all others (at values of HDO<sub>2</sub> equal to 6–7 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>). At values of HDO<sub>2</sub> equal to 2–3 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>, the values of hepatic lactate uptake became negative, signifying that the liver began to release rather than to metabolize lactate. There were no significant differences among the groups in the values of hepatic oxygen delivery at which the liver started to release lactate (fig. 3). A relatively linear relationship was observed between hepatic oxygen uptake and hepatic lactate uptake in all groups of

animals (fig. 4). There were no significant differences between the values of hepatic oxygen uptake at which the livers started to release lactate among the groups (fig. 4).

#### THE RELATIONSHIP BETWEEN HEPATIC VENOUS BLOOD OXYGEN AND HEPATIC OXYGEN DELIVERY, HEPATIC OXYGEN UPTAKE, AND HEPATIC LACTATE UPTAKE (STAGES 1–5)

There were linear and strong associations between the values of hepatic oxygen delivery and hepatic venous oxygen tension or saturation in every group (fig. 5; *r* = 0.96; *P* < 0.0001). When oxygen tension in hepatic venous blood reached 25–28 mmHg, hepatic oxygen uptake started to decrease (fig. 6) and became oxygen delivery dependent. The liver stopped metabolizing and started to release lactate at an oxygen tension of 10–13 mmHg in hepatic venous blood in all five groups studied without significant differences among the groups (fig. 7).

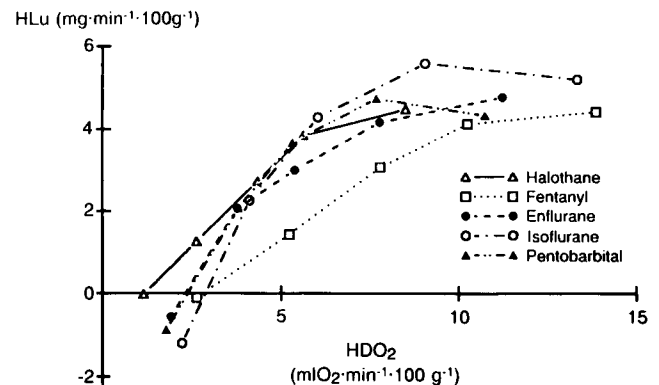


FIG. 3. The changes in hepatic lactate uptake (HLu) during stepwise decrease in hepatic oxygen delivery (HDO<sub>2</sub>). At values of HDO<sub>2</sub> = 2–3 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>, the values of HLu became negative signifying that the liver stopped metabolizing and started to release lactate.

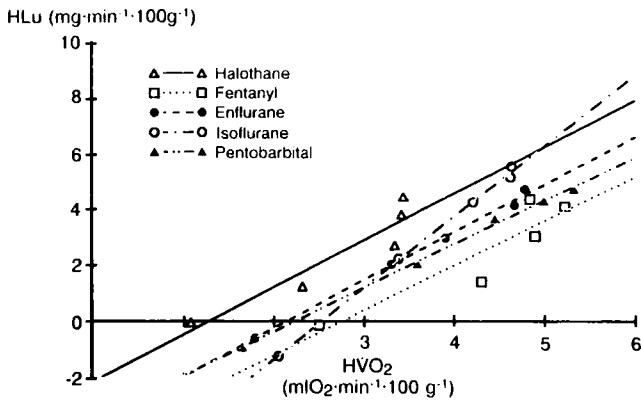


FIG. 4. The relationship between hepatic oxygen uptake ( $H\dot{V}O_2$ ) and hepatic lactate uptake (HLu). The points of intersection between the regression lines for five anesthetics and zero line for HLu identifies the critical values of  $H\dot{V}O_2$  at which liver stopped to metabolize and started to release lactate.

Discussion

METHODOLOGIC REMARKS

The pig is a better anatomic and physiologic model for studies on the cardiovascular and digestive system than the dog; the splanchnic circulation, and especially the liver circulation, of pigs is remarkably similar to that of humans.<sup>14-16</sup> We used the Hanford strain of minipigs weighing 20-31 kg, age 6-7 months from Charles River Laboratories. These pigs are maturer than normally used younger pigs with the same weight. This model also provided an opportunity to produce hepatic ischemia *in vivo* without congestion or ischemia in the preportal tissues. The values of hepatic arterial blood flow and portal blood

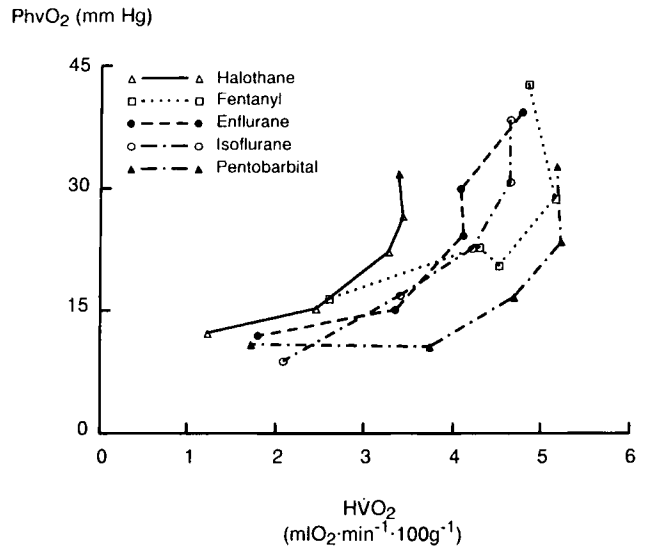


FIG. 6. The relationship between oxygen tension in hepatic venous blood ( $PhvO_2$ ) and hepatic oxygen uptake ( $H\dot{V}O_2$ ) during stepwise decrease in hepatic oxygen delivery when oxygen saturation in hepatic venous blood reached 25-28% mmHg, hepatic oxygen uptake started to decrease and become oxygen delivery dependent signifying the point of critical hepatic oxygen delivery.

flow in anesthetized different animals range from 9.4-70  $ml \cdot min^{-1} \cdot 100 g^{-1}$  and from 30-93  $ml \cdot min^{-1} \cdot 100 g^{-1}$ , respectively.<sup>17</sup> In pigs, these values range from 12-33  $ml \cdot min^{-1} \cdot 100 g^{-1}$  for hepatic arterial blood flow and from 47-75  $ml \cdot min^{-1} \cdot 100 g^{-1}$  for portal blood flow.<sup>18-25</sup> Values of flow observed in our stage 1 of observations are compatible with the reported ranges.

Innervation of the hepatic vasculature is rich and quite complex and mainly achieved through the two plexuses

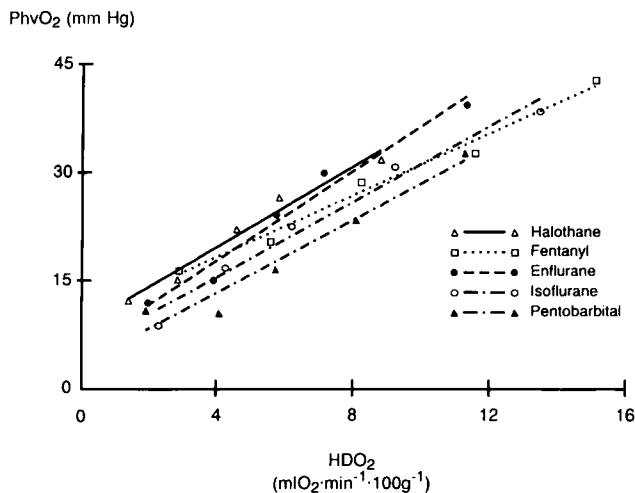


FIG. 5. The relationship between hepatic oxygen delivery ( $HDO_2$ ) and oxygen tension in hepatic venous blood ( $PhvO_2$ ) during stepwise decrease in  $HDO_2$ .  $r = 0.96$ ,  $P < 0.0001$  for all five groups.

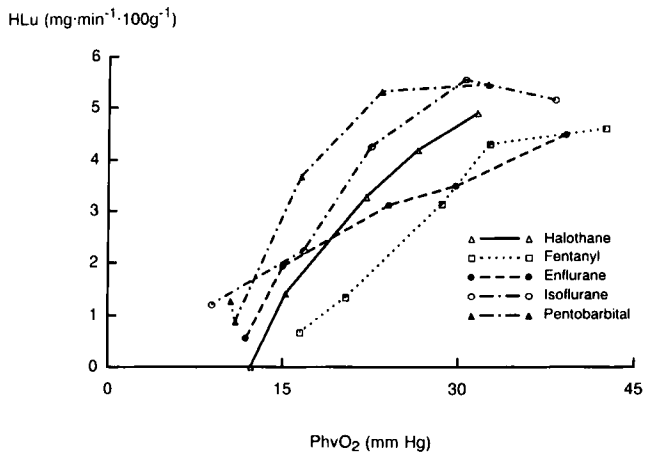


FIG. 7. The relationship between oxygen tension in hepatic venous blood ( $PhvO_2$ ) and hepatic lactate uptake (HLu). The liver started to release lactate at  $PhvO_2$  equal to 10-13% mmHg without significant differences among the groups.

that freely mingle in the region where the hepatic artery and portal vein run in close proximity.<sup>26</sup> Therefore, the fact that the hepatic artery and portal vein were transected most probably did not affect the innervation of the liver. Also, if some degree of denervation occurred in our preparation, the degree of the denervation was similar in all groups; therefore, the differences among the groups were most probably related to the anesthetics rather than to the degree of denervation. Last, and more importantly, hepatic circulation is regulated to a great extent by metabolic and hormonal factors, and changes in systemic hemodynamics. In this regard, the surgical preparation used in this study obviously interfered with normal blood flow. However, this interference was similar in all groups studied and the main thrust of this study was to examine the possible protective effect of anesthetics on the liver during hepatic oxygen deprivation. The extent of hepatic circulation disturbances, which was most probably similar in all groups, were not very important in conditions of induced severe hepatic hypoxia. The effects of four widely used drugs, as well as pentobarbital as a control, were examined in conditions of stepwise decrease in hepatic oxygen supply. The main limitation of the study is that the effect of only one dose of each anesthetic was examined. However, the main thrust of the study was to provide anesthetic management as close to clinically relevant conditions as possible, and to find the anesthetic that would provide the most favorable relationship between hepatic oxygen supply and demand.

End-expired concentrations of volatile anesthetics were maintained at approximately 1 MAC value determined with the tail clamp.<sup>14,27-29</sup> This method apparently underestimates the MAC values determined with the dew claw clamp.<sup>27</sup> One way or the other, the concentrations most probably were equipotent because the values of MAC used in this study were determined by using the same method of tail clamping. More importantly, the values of mean arterial pressure during the study were adequate and relatively similar, particularly among the groups of animals anesthetized with volatile anesthetics, reinforcing the clinical relevance of the experiments. Another limitation of the study is related to the absence of a true control group where a decrease in hepatic oxygen supply would be provided without anesthesia. For obvious reasons, experiments with hepatic ischemia could not be performed on unanesthetized animals. Finally, the effects of residual concentrations of methohexital on overall results cannot be ruled out. However, a relatively short half-life of methohexital<sup>30</sup> and presence of certain differences among the groups suggest that the role of methohexital in these experiments was negligible. Pancuronium used for muscle paralysis in this study probably did not cause

any significant changes in hepatic circulation and oxygenation.<sup>31,32</sup>

#### HEPATIC OXYGEN DELIVERY-UPTAKE RELATIONSHIPS

In all five groups studied, hepatic oxygen delivery-uptake relationships could be described in two phases: hepatic oxygen uptake being independent of hepatic oxygen delivery (phase I, stages 1 and 2) and when hepatic oxygen uptake was oxygen delivery dependent (phase II, stages 3, 4, and 5). During phase I, hepatic oxygen uptake remained constant over a wide range of hepatic oxygen delivery and apparently reflects the situation of no oxygen deficit and represents hepatic oxygen demand. When decreasing hepatic oxygen delivery reached a certain point, defined as critical hepatic oxygen delivery, hepatic oxygen uptake started to decrease proportionally to the reduction in hepatic oxygen delivery. During this phase, the liver would likely be hypoxic. A biphasic relationship between hepatic oxygen delivery and uptake has been observed in isolated hepatocytes,<sup>33</sup> isolated perfused liver,<sup>34</sup> and in the liver perfused by pumps *in situ*.<sup>35</sup>

Thus, the plot of the hepatic oxygen delivery-uptake relationship provides information on hepatic oxygen delivery, hepatic oxygen demand, and critical hepatic oxygen delivery. The present study demonstrates certain effects of the examined anesthetics on these three rather important variables.

The study demonstrated significantly greater values of hepatic oxygen delivery during anesthesia with isoflurane or fentanyl than the values observed during anesthesia with halothane at the first stage of experiments before stepwise decrease in hepatic oxygen delivery was begun (table 1, fig. 2). However, the values of hepatic oxygen demand (actually the values of hepatic oxygen uptake during phase I) were smaller in the halothane group than in the remaining four groups (table 1, fig. 2). The differences between values of hepatic oxygen delivery and hepatic oxygen demand, or in other words, between hepatic oxygen delivery and critical hepatic oxygen delivery, characterize the margin of safety for the hepatic oxygen supply-demand relationship. The study suggests that anesthesia with fentanyl, and possibly isoflurane, might be associated with a more beneficial hepatic oxygen-demand relationship, or in other words, with a greater margin of safety than anesthesia with other drugs. It is interesting to note that in this study as well as in many others, anesthesia with halothane was associated with the smallest values of hepatic oxygen delivery in conditions of non-restricted hepatic blood flow.<sup>1</sup> However, in this study, halothane anesthesia was also associated with the smallest values of hepatic oxygen demand (fig. 2). Therefore, the

overall hepatic oxygen supply-demand relationship during halothane did not differ significantly from the enflurane or pentobarbital groups. This study did not address the question of whether this decrease in hepatic oxygen demand under halothane is beneficial for the liver. Furthermore, some studies *in vitro* suggest that a halothane-induced decrease in hepatic oxygen demand may result from impaired electron transport and mitochondrial function in the liver rather than from a decreased energy requirement.<sup>9,36</sup> On the other hand, it has been demonstrated that halothane exerts a beneficial effect on the survival of rats following acute intestinal ischemia,<sup>37</sup> which may be attributed, at least partially, to the decrease in hepatic oxygen requirements associated with halothane. It appears at present, that regardless of the intimate mechanism of halothane-induced reduction in hepatic oxygen demand, halothane decreases hepatic oxygen delivery to a similar or possibly greater extent than hepatic oxygen demand and therefore does not provide the most beneficial hepatic oxygen supply-demand relationship. The overall hepatic oxygen supply-demand relationship is probably more beneficial during anesthesia with isoflurane and fentanyl than with other anesthetics.

#### HEPATIC LACTATE UPTAKE

Hepatic lactate uptake depends on the hepatic oxygen supply-demand relationship. A strong linear relationship between hepatic lactate uptake and hepatic oxygen uptake in dogs anesthetized with barbiturates has been demonstrated during graded hypoxemia.<sup>38</sup> This is not surprising because the pathway of lactate metabolism by the liver is gluconeogenesis in which oxygen and ATP are required for the synthesis of glucose. Therefore, hepatic lactate and oxygen uptake are closely linked and subsequently, when hepatic oxygen uptake is reduced, the liver stops metabolizing and starts to release lactate. Probably at this point, the liver switches metabolism from gluconeogenesis to glycolysis, reflecting anaerobic metabolism. The values of critical hepatic oxygen uptake, defined as values of hepatic oxygen uptake at which the liver stops to metabolize and starts to release lactate (fig. 4), in our study are similar to those in the study by McDonald *et al.*<sup>38</sup> These values are between 2–3 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup> for all groups except halothane, where the values are slightly greater than 1 mlO<sub>2</sub> · min<sup>-1</sup> · 100 g<sup>-1</sup>. This observation is consistent with the hypothesis that halothane decreases hepatic oxygen and energy requirements and thereby might provide some protection for the liver against ischemic insult. These data (concerning the possible protective effect of halothane) do not imply yet that halothane should be used in clinical practice for liver protection from possible or ex-

pected hypoxia because halothane also decreases hepatic oxygen supply quite dramatically and therefore does not offer noticeable advantages compared with other anesthetics.

#### HEPATIC VENOUS OXYGEN

The values of oxygen tension in hepatic venous blood corresponding to critical hepatic oxygen delivery were around 25–28 mmHg in each group without significant differences among the groups (fig. 6).

In clinical situations it is difficult, if not impossible, to continuously monitor hepatic oxygen supply-demand relationship. This study demonstrated a strong association between oxygen saturation, tension or content in the hepatic venous blood, and hepatic oxygen delivery, hepatic oxygen uptake or hepatic lactate uptake. This strong association suggests that in some clinical situations where hepatic oxygen delivery-demand relationship and hepatic function seem to be in jeopardy, the oxygen saturation or tension in the hepatic venous blood might be monitored as an indicator of adequacy of the hepatic oxygen supply.

In summary, this study demonstrated a biphasic relationship between hepatic oxygen delivery and uptake. Among the five anesthetics studied, isoflurane and fentanyl provided the greatest values of hepatic oxygen delivery and the most beneficial hepatic oxygen supply-demand relationship. Halothane decreased hepatic oxygen demand and might provide some protection from hepatic oxygen deprivation; however, the decrease in hepatic oxygen delivery produced by halothane was similar or greater than a decrease in hepatic oxygen demand. Therefore, halothane might not be an anesthetic of choice for surgical procedures where hepatic hypoxia is expected. The possibility cannot be ruled out that halothane can protect the liver better than other anesthetics during total anoxia.

The study demonstrated a close association between oxygen content, saturation, and tension in hepatic venous blood and hepatic oxygen delivery, uptake or hepatic lactate uptake. Therefore, oxygen content in hepatic venous blood may be considered as an indicator of adequacy of hepatic oxygen supply.

#### References

1. Gelman S: General anesthesia and hepatic circulation. *Can J Physiol Pharmacol* 65:1762–1779, 1987
2. Gelman S, Dillard E, Bradley EL Jr: Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. *Anesth Analg* 66:936–943, 1987
3. Gelman S: Disturbances in hepatic blood flow during anesthesia and surgery. *Arch Surg* 111:881–883, 1976
4. Bohrer SL, Rogers EL, Koehler RC, Traystman RJ: Effect of hy-



- povolemic hypotension and laparotomy on splanchnic and hepatic arterial blood flow in dogs. *Curr Surg* 38:325-328, 1981
5. Michenfelder JD: Anesthesia and the brain. Clinical functional, metabolic, and vascular correlates. New York, Churchill Livingstone, 1988, pp 83-87, 100-106
  6. Kashimoto S: Effects of isoflurane on myocardial metabolism during postschaemic reperfusion in the rat. *Acta Anaesthesiol Scand* 32:199-202, 1988
  7. Middleton MD, Roth GJ, Smuckler EA, Nyhus LM: The effect of high concentration of halothane on the isolated perfused bovine liver. *Surg Gynecol Obstet* 122:817-825, 1966
  8. Coultas RJ, Strunin L, Walker WD, Strunin JM, Simpson R and BR: A comparison of the effects of halothane and methoxyflurane on the isolated perfused canine liver. *Br J Anaesth* 41:490-491, 1969
  9. Biebueck JF, Lund P, Krebs HA: The effects of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) on glycolysis and biosynthetic process of the isolated perfused rat liver. *Biochem J* 128:711-720, 1972
  10. Michiels M, Hendriks R, Heykants J: Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetics profile in man. *J Pharm Pharmacol* 35:86-93, 1983
  11. Marbach EP, Weil MH: Rapid enzymatic measurement of blood lactate and pyruvate. *Clin Chem* 13:314-325, 1967
  12. Snedecor GW, Cochran WG: Statistical Methods. Ames, Iowa State University Press: 1980, pp. 215-237
  13. Samsel RW, Schumacker PT: Determination of the critical O<sub>2</sub> delivery from experimental data: sensitivity to error. *J Appl Physiol* 64:2074-2082, 1988
  14. 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
  15. Mount LE, Ingram DL: The Pig as a Laboratory Animal. London, Academic Press, 1971
  16. Dodds WJ, Hsu C-K: Introductions: Strengths and limitations of the pig as an animal model. The pig model for biomedical research. *Fed Proc* 41:247-256, 1982
  17. Richardson PDI, Withrington PG: Liver blood flow: I. Intrinsic and nervous control of liver blood flow. *Gastroenterology* 81:159-173, 1981
  18. Norlen K: Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerin. *Br J Anaesth* 61:186-193, 1988
  19. Feuk U, Jakobson S, Norlen K: The effects of alpha adrenergic blockade on central haemodynamics and regional blood flows during positive pressure ventilation. *Acta Anaesthesiol Scand* 31:748-755, 1987
  20. Feuk U, Jakobson S, Norlen K: Central haemodynamics and regional blood flows during thoracic epidural analgesia combined with positive pressure ventilation. *Acta Anaesthesiol Scand* 31:479-486, 1987
  21. Bulkley GB, Oshlma A, Balley RW: Pathophysiology of hepatic ischemia in cardiogenic shock. *Am J Surg* 151:87-97, 1986
  22. Hickman R, Saunders SJ, Terblanche J: Liver function in the pig: Total hepatic and portal flow values in vivo. *S Afr Med J* 48:1197-1200, 1974
  23. Lindberg B, Darle N: The effect of dextran 40 and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. *J Surg Res* 23:264-273, 1977
  24. Lindberg B, Darle N: Effect of glucagon on hepatic circulation in the pig. *Arch Surg* 111:1379-1383, 1976
  25. 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
  26. Lutt WW: Afferent and efferent neural roles in liver function. *Prog Neurobiol* 21:323-348, 1983
  27. Eger EL II, Johnson BH, Weiskopf RB, Holmes MA, Yasuda N, Targ A, Rampil IJ: Minimum alveolar concentration of I-653 and isoflurane in pigs: Definition of a supramaximal stimulus. *Anesth Analg* 67:1174-1176, 1988
  28. Eisele PH, Talken I, Eisele JH Jr: Potency of isoflurane and nitrous oxide in conventional swine. *Lab Anim Sci* 35:76-78, 1985
  29. Tranquilli WJ, Thurmon JC, Benson GJ, Steffey EP: Halothane potency in pigs (*Sus scrofa*). *Am J Vet Res* 44:1106-1107, 1983
  30. Breimer DD: Pharmacokinetics of methohexitone following intravenous infusion in humans. *Br J Anaesth* 48:643-649, 1976
  31. Varma YS, Sharma PL, Minocha KB: Comparative evaluation of cerebral and hepatic blood flow under d-tubocurarine and pancuronium in dogs. *Indian J Med Res* 66:317-322, 1977
  32. Dhasmana KM, Verdouw PD, Prakash O, Saxena PR: Effect of neuromuscular blocking agents pancuronium bromide and its monoquaternary analogue org NC 45 on regional blood flow and cardiac metabolism in pigs. *Drug Dev Res* 2:393-402, 1982
  33. Longmuir IS: Respiration rate of rat-liver cells at low oxygen concentrations. *Biochem J* 65:378-382, 1957
  34. Meren H, Matsumura T, Kauffman FC, Thurman RC: Relationship between oxygen tension and oxygen uptake in the perfused rat liver. *Adv Exp Med Biol* 200:467-476, 1986
  35. Lutz J, Henrich H, Bauereisen E: Oxygen supply and uptake in the liver and the intestine. *Pflugers Arch* 360:7-15, 1975
  36. Miller RN, Hunter FE Jr: The effect of halothane on electron transport, oxidative phosphorylation, and swelling in rat liver mitochondria. *Mol Pharmacol* 6:67-77, 1970
  37. Bavister PH, Longnecker DE: Influence of anesthetic agents on the survival of rats following acute ischaemia. *Br J Anaesth* 51:921-925, 1979
  38. MacDonald AC, Marble AE, Perkins JG: Hepatic blood flow and metabolism. *Arch Surg* 114:616-622, 1979