Splanchnic Oxygen Consumption and Hepatic Surface Oxygen Tensions during Isoflurane Anesthesia

Peter F. Conzen, M.D.,* Jonny Hobbhahn, M.D.,† Alwin E. Goetz, M.D.,* Helmut Habazettl, M.D.,* Thomas Granetzny, M.D.,† Klaus Peter, M.D.,† Walter Brendel, M.D.§

Blood flow to and oxygen consumption of the splanchnic organs were determined together with hepatic surface oxygen tensions in 18 mongrel dogs anesthetized with the long-acting narcotic piritramid. Twelve animals also received 0.7 Vol% and 1.4 Vol% isoflurane; six time-related controls received piritramid only. Surgical preparation consisted of a left thoracotomy for inserting a catheter into the left atrium for microsphere injections and for gaining access to the hepatic surface through an incision in the diaphragm. Parameters in the animals receiving isoflurane were recorded at three stages: stage 1—piritramid anesthesia after surgical preparation; stage 2—60 min after addition of 0.7 Vol% (end-expiratory) isoflurane; stage 3—60 min after addition of 1.4 Vol% (end-expiratory) isoflurane. Hepatic surface oxygen tension was determined at each stage using an eight-channel oxygen sensitive electrode. Mean arterial pressure and cardiac output decreased during both stages with isoflurane; hepatic arterial inflow remained constant. Portal blood flow and, hence, total hepatic inflow decreased significantly. An unchanged splanchnic O₂ consumption induced lower hepatic venous p ao values 40 ± 1 mmHg at control, 35 ± 2 mmHg, and 31 ± 2 mmHg (mean ± SEM; both P < 0.05) during isoflurane. A concomitant decrease of hepatic surface p ao values indicated an altered tissue oxygenation. The percentage of hepatic surface p ao values in the lowest p ao range (0–5 mmHg) increased significantly from 8.4 to 20.3% during 1.4 Vol% isoflurane; the percentage of values of 0 mmHg increased from 2.4 to 9.8% during 1.4 Vol%. No changes of these parameters were detected in the control animals during the 3-h observation period. These results indicate that isoflurane significantly altered total hepatic blood flow, whereas oxygen consumption of the splanchnic viscera remained unchanged. This decreased hepatic blood flow was associated with a decrease of both hepatic venous p ao and hepatic surface oxygen tension that was more pronounced at the higher isoflurane concentration. (Key words: Anesthetics, Intravenous: piritramid. Anesthetics, volatile: isoflurane. Liver blood flow; surface p ao. Measurement techniques: radioactive microspheres.)

The effects of halothane and enflurane on splanchnic blood flow and splanchnic oxygen consumption have been extensively studied. While both volatile anesthetics are reported to reduce splanchnic blood flow, their effects on splanchnic visceral oxygen consumption are less clearly defined.2–5 There is no doubt, however, that both, halothane and enflurane induce a lower ratio of oxygen supply to consumption and a higher oxygen extraction within the splanchnic vascular bed.6–10

Few data are available, concerning the effects of isoflurane on these parameters. Previous studies on hepatic blood flow by Gelman et al.7,8 in dogs and Lundeen et al.9 in pigs have shown a variable decrease of total perfusion. In contrast, Szydlo and Longnecker noted well-maintained hepatic artery and portal vein blood flow (hence total hepatic blood flow) when they compared the awake states to anesthesia with 1.4 Vol% isoflurane in normovolemic and in hemorrhaged rats.10 In a recent study in pigs, Gelman et al. noted diverse effects of isoflurane on the hepatic oxygen supply to demand ratio depending on the decrease of arterial blood pressure.11 In this study, we assessed splanchnic blood flow and oxygen consumption of the splanchnic organs in anesthetized dogs without isoflurane and with two steady-state concentrations of isoflurane (0.7 and 1.4 Vol% end-expiratory). Blood flow to the splanchnic organs and distribution of cardiac output were determined by radioactive microsphere technique.12

As cellular oxygen supply and, hence, tissue oxygenation is not only dependent on the total amount of oxygen delivered, but also on local metabolic demands or microcirculatory blood flow distribution, we assessed alterations of hepatic tissue oxygen supply by use of an oxygen sensitive multiwire surface electrode.15

Materials and Methods

Eighteen mongrel dogs of either sex varying in body weight from 25 to 36 kg (mean 28.9 kg) were used in these experiments. All experiments were approved by the animal care committee. Anesthesia was induced after overnight fasting with intravenous ketamine (10 mg/kg), flunitrazepam (0.01 mg/kg), and atropine (0.5 mg) and maintained by infusion of piritramid (1 mg·kg⁻¹·h⁻¹). Following endotracheal intubation, the lungs were ventilated mechanically with a mixture of nitrous oxide in oxygen (Servo-Ventilator 900B, Siemens, Erlangen, West Germany). The inspiratory oxygen fraction was adjusted
to maintain arterial $pO_2$ between 90 and 110 mmHg. At a rate of 15 breaths per minute, tidal volume was set to keep end-expiratory $CO_2$ at 4.5 Vol%. The animals were placed on a heating pad maintaining core temperature during the experimental period. Additional infrared lights were used whenever necessary.

**Operative Procedure**

A polyethylene catheter was inserted into the abdominal aorta via the femoral artery and a catheter tip manometer (Millar Instruments, Houston, TX) in the left ventricle through a carotid artery. External jugular veins were used for inserting a 7-french Swan-Ganz catheter into the pulmonary artery and a 2 mm outer diameter tubing with sideholes at its tip into a hepatic vein. These catheters were advanced under fluoroscopic guidance and correct position periodically reevaluated. By injecting contrast media we insured that the most proximal sidehole of the hepatic catheter was at least 2–3 cm into the hepatic vein. The thoracic cavity was then entered through a left lateral incision in the fifth intercostal space. A catheter was inserted into the left atrium via its auricle for determination of left atrial pressure and for injection of radioactive microspheres. The liver was exposed through an incision in the diaphragm, carefully avoiding bleeding or irritation of the hepatic surface.

**Cardiac Output and Pressure Measurement**

Cardiac output (CO) was determined by thermodilution technique (Gould-Statham SP 1425, Statham Instruments, Oxnard, CA). The mean value of triplicate injections of 5 ml of ice cold saline was considered to reflect actual cardiac output if the measurements were within a range of ±5% from the calculated mean. Aortic, pulmonary arterial, and left atrial catheters were connected to Statham P234D pressure transducers, and the signals were amplified and recorded.

**Measurement of Organ Blood Flow**

The reference withdrawal method was applied to measure blood flow to splanchic organs with radioactive microspheres. We used standard carbonized microspheres with mean diameters of 15 μm labeled with 141-Ce, 51-Cr, 85-Sr, 95-Nb (3-M Company, St. Paul, MN).

For each blood flow determination, 2.5–4.0 million microspheres suspended in sterile physiologic saline were injected. The microspheres were injected over 25–50 s through the left atrial catheter, which was subsequently flushed with 10 ml of warm saline. An arterial reference sample was withdrawn at a constant rate from the abdominal aorta by use of a Harvard pump (6.4 ml/min). Withdrawal was started 20 s prior to the microsphere injection and continued for 120 s thereafter. Usually, injections were not followed by hemodynamic changes, but in a few cases there was a 5–10-mmHg decrease in systolic blood pressure for a few seconds. Cardiac arrhythmias were not observed. Homogeneous microsphere distribution was verified post mortem by comparing the left and right renal cortical blood flow values. Hepatic arterial resistance was calculated as the mean arterial to right atrial pressure gradient divided by hepatic arterial flow. Preportal resistance was calculated as the quotient of the abdominal aortic to portal vein pressure difference and total preportal flow, assuming a portal venous pressure of 10 mmHg.

**Determination of Hepatic Surface Oxygen Tension**

The method used herein to determine oxygen pressure fields has been described in detail. In brief, it consists of a Clark-type electrode with eight thin platinum cathodes and one Ag/AgCl anode. The electrode is covered with a teflon membrane and placed on the surface of the liver. The weight of the electrode is low (1.5 g), so that microcirculatory disturbances or ischemia due to its pressure are avoided. At a constant polarization voltage of approximately −700 mV, a single platinum wire (diameter 15 μm) registers a reduction current linearly dependent on the partial pressure of oxygen. The mean distance between 2 wires is 100 μm. The radius of the oxygen sensitive surface area of the different platinum wires depends on the thickness of the membrane used and is 20–25 μm with a membrane of 25 μm. Due to the relatively large hemispheric catchment area, the electrode measures averaged oxygen pressures on liver cells, capillaries, and small pre- and postcapillary vessels. The results are best presented as frequency distribution curves, since mean values do not necessarily change from one measuring situation to another, although a definite biologic change may have occurred. At each end-expiratory isoflurane concentration (0, 0.7, and 1.4 Vol%), a total of 80–100 individual oxygen pressure measurements were obtained at 10–15 different electrode locations on the hepatic surface. The distribution of these values reflects tissue oxygenation, giving the net result of nutritive blood flow and tissue oxygen consumption. The electrode is calibrated before and after each recording with three different concentrations of oxygen: 0%, 5%, and 10%. The reduction current of the electrode is linear within this range (using calibration gases in steps of 1 Vol% $O_2$). Neither isoflurane nor enflurane have any influence on the electrode signal.

Reduction current signals from each of the eight channels are amplified, digitized, and processed using a PDP 11/23 computer (Digital Equipment Corporation, Maynard, MA). Histograms are constructed using $pO_2$ ranges of 5 mmHg to describe the distribution of hepatic surface oxygen pressure values.
PROCESSING OF TISSUE

At the end of each experiment, the dog was killed by injection of potassium chloride and the splanchnic organs removed. After discarding fat tissue, the organs were weighed. Small and large intestine were divided into eight and three segments of equal size, respectively. In five specimens of each segment, together with ten specimens of spleen and pancreas and 15 specimens of gastric tissue, the amounts of radioactivity were determined. Each sample was weighed and placed in vials for gamma counting along with the arterial reference samples. Portal flow was calculated as the sum of blood flow through these organs. Hepatic arterial flow was determined after counting 30 specimens of hepatic tissue (five of each lobe). A 1024-channel multiple region-of-interest gamma counter (Model 9520, Packard Instruments, Downers Grove, IL) with a 3-inch crystal was employed. The data were corrected for background and cross-over activity by use of a digital PDP 11/34 computer (Digital Equipment Corporation, Maynard, MA). The total number of microspheres trapped and blood flow per gram tissue were determined in each individual sample.

BLOOD GAS ANALYSIS

Blood gas parameters and acid-base status in arterial, hepatic-venous, and mixed-venous blood samples were derived from a gas analyzer (Analysator D, Eschweiler & Co., Kiel, West Germany). Hemoglobin concentrations were measured by cyan methemoglobin method. All determinations were performed twice. Oxygen saturation was calculated from temperature and pH-corrected \( P_{O_2} \) data applying a p50 of 27 mmHg. Oxygen content of the blood samples was calculated from the following equation:

\[
O_2 \text{content} = Hb \text{ concentration} \times O_2 \text{ saturation} \times 1.34
\]

Data were corrected for temperature. Splanchnic oxygen consumption was calculated by the arterial-hepatic venous oxygen content difference times total splanchnic blood flow and normalized for body weight. Normalized systemic oxygen consumption was calculated by the arterial minus mixed-venous oxygen content difference times cardiac output and divided by body weight.

EXPERIMENTAL PROTOCOL

At the end of the surgical preparation period, nitrous oxide was discontinued and anesthesia maintained by iv piritramid. Constant \( p_{A\text{CO}_2} \) of 100 mmHg required inspiratory oxygen fractions of 0.25–0.35. The animals' vital signs were allowed to stabilize for 30 min. Baseline recordings of hemodynamics, blood gas parameters, hepatic surface \( P_{O_2} \), and splanchnic blood flow were then obtained. In the animals of the control group (no isoflurane given), measurements were obtained after 60 and 120 min without any change in the experimental setup. Measurements in the isoflurane animals were repeated after 60 min ventilation with 0.7 Vol.% while piritramid infusion was continued at an unchanged rate. This was followed by a second stage of observation, in which 1.4 Vol.% isoflurane was administered for another 60 min. End-expiratory isoflurane concentrations were measured using a multigas analyzer (EMMA, Engström Medical AB, Sweden). The EMMA sensor was separated from the expired air by a humidity retaining "artificial nose" (Edith, Engström) and zeroed with the animal's expired air. Measurements were begun after a warm-up period of at least 30 min. The EMMA was calibrated using a standard calibration gas according to factory specifications.

Left atrial pressures were held constant during the time course of the experiments by transfusion with crystalloid solutions and with autologous blood that had been withdrawn 1–2 weeks before the experiments. About 35 ml of autologous blood were replaced at each experimental step for correction of losses due to blood sampling.

STATISTICAL ANALYSIS

Summary data of hemodynamic and blood gas variables are expressed as mean ± standard error of the mean (SEM). \( P_{O_2} \) histograms were analyzed according to their frequency of values of 0 mmHg and by the number of measuring points in the lowest \( P_{O_2} \) class (0–5 mmHg), because these are most relevant to indicate deterioration of tissue oxygenation. Statistically significant differences between baseline and the two levels of isoflurane were evaluated by Friedman's ranked analysis of variance. This was followed by corrected Wilcoxon and Wilcoxon multiple comparisons to determine which experimental steps were different from each other. Inter-group differences in the \( P_{O_2} \) histograms were determined by Chi-square test; hemodynamic and blood gas variables at corresponding experimental steps were compared by Wilcoxon U-test. A P value < 0.05 was considered statistically significant.

Results

HEMODYNAMIC PARAMETERS

Results from the piritramid anesthetized control animals are summarized in table 1; significant hemodynamic changes over time were absent. Table 2 lists hemodynamic parameters obtained in the isoflurane-treated dogs during 0 (control), 0.7, and 1.4 Vol.% of isoflurane. Heart rate in these animals remained essentially unchanged. Despite constant left atrial pressures of about 7 mmHg, cardiac output decreased to 90% and 80% of its initial value. Both mean arterial pressure and systemic vascular resistance were reduced significantly at both concentrations of isoflurane.
TABLE 1. Hemodynamic Parameters, Splanchnic Blood Flow, and Oxygen Consumption in the Control Group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 hour</th>
<th>2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (min⁻¹)</strong></td>
<td>89 ± 6</td>
<td>81 ± 6</td>
<td>83 ± 5</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>90 ± 5</td>
<td>85 ± 4</td>
<td>85 ± 4</td>
</tr>
<tr>
<td><strong>CO (l·min⁻¹)</strong></td>
<td>5.8 ± 0.4</td>
<td>5.3 ± 0.2</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td><strong>SVR (dyn·sec·cm⁻⁵)</strong></td>
<td>1917 ± 262</td>
<td>2030 ± 175</td>
<td>1995 ± 105</td>
</tr>
<tr>
<td><strong>Syst. O₂C</strong></td>
<td>4.65 ± 0.57</td>
<td>4.37 ± 0.18</td>
<td>4.57 ± 0.35</td>
</tr>
<tr>
<td>(ml·min⁻¹·kg⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Q₅₀ (ml·min⁻¹·100 g⁻¹)</strong></td>
<td>117 ± 18</td>
<td>119 ± 16</td>
<td>121 ± 13</td>
</tr>
<tr>
<td><strong>hep. ven. P₀₂ (mmHg)</strong></td>
<td>37 ± 3</td>
<td>56 ± 3</td>
<td>38 ± 3</td>
</tr>
<tr>
<td><strong>hep. art R</strong></td>
<td>2.52 ± 0.51</td>
<td>2.83 ± 0.59</td>
<td>2.46 ± 0.60</td>
</tr>
<tr>
<td>(mmHg·min·m⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>preportal R.</strong></td>
<td>137 ± 15</td>
<td>124 ± 11</td>
<td>116 ± 8</td>
</tr>
<tr>
<td><strong>hep. surf. P₀₂ 0-5 mmHg (%)</strong></td>
<td>5.7 ± 2.6</td>
<td>0.6 ± 0.4</td>
<td>2.7 ± 1.6</td>
</tr>
<tr>
<td><strong>hep. surf. P₀₂ 0 mmHg (%)</strong></td>
<td>0</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.3</td>
</tr>
</tbody>
</table>

HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance; Syst. O₂C = whole body oxygen consumption; Q₅₀ = total hepatic blood flow; Splan O₂C = oxygen consumption of the splanchnic organs normalized per kg body weight; hep. ven. P₀₂ = P₀₂ in the hepatic vein; hep. art. R. = hepatic arterial resistance; preportal R. = vascular resistance of the preportal bed; hep. surf. P₀₂ 0-5 mmHg = relative number of measurements in the lowest P₀₂ range (0–5 mmHg) of hepatic surface histograms; hep. surf. P₀₂ 0 mmHg = number of zero mmHg P₀₂ values on the hepatic surface. All values are given as means ± SEM.

**Splanchnic Blood Flow**

Hepatic arterial and splanchnic blood flow values in the control animals remained constant over the 3-h period (fig. 1; table 1). During isoflurane, microsphere determinations of hepatic arterial inflow did not reveal significant changes, nor were the results different from the control group (fig. 2). The fraction of cardiac output received by the liver through the hepatic artery remained between 4.0 and 4.5%. Calculated resistance with hepatic arterial inflow data decreased from 1.3 ± 0.27 to 0.62 ± 0.1 and 0.71 ± 0.17 (mmHg·min·m⁻¹) and preportal resistance decreased from 159 ± 17 to 129 ± 13 and 101 ± 11 (mmHg·min·l⁻¹) during 0.7 and 1.4 Vol% isoflurane, respectively.

Portal flow was significantly decreased from 95 ± 13 to 77 ± 10 and 80 ± 13 (ml·min⁻¹·100 g⁻¹) with 0.7 and 1.4 Vol% isoflurane, respectively; total hepatic flow was similarly decreased to the same extent at both isoflurane concentrations (fig. 2; table 2). Linear regression analysis in the isoflurane group revealed significant correlations for total splanchnic flow with cardiac output (r = 0.6 for Q₅₀ = 10.2 + 0.72 × CO; P < 0.001) and mean arterial pressure (r = 0.5 for Q₅₀ = 37 + 0.84 × MAP; P < 0.01). Left and right kidney cortical flow values did not differ more than 10%, signifying homogeneous distribution of microspheres.

**Hepatic Tissue Oxygenation**

Calculated oxygen uptake of the splanchnic bed normalized for body weight remained essentially unchanged in both groups. However both, hepatic venous P₀₂ and tissue P₀₂ decreased in the animals receiving isoflurane. P₀₂ histograms of the control animals were unchanged during the observation period (fig. 3). In contrast, summary histograms obtained on the liver surface were slightly altered with 0.7 Vol. % isoflurane. An obvious leftward shift, i.e., to a lower mean P₀₂, was detected with 1.4 Vol. % isoflurane (fig. 4). A significantly increased number of P₀₂ values in the lowest histogram range between 0 and 5 mmHg was observed in animals breathing 1.4% Vol. %. Comparison between both groups revealed a significant difference already during 0.7 Vol. %. Zero mmHg P₀₂ values were unchanged with 0.7 Vol. % isoflurane. Statistical significance (as compared to the control group, as well as to baseline before isoflurane) was reached at the higher isoflurane level. Whole body oxygen consumption was decreased significantly during isoflurane. No changes of these parameters were detected in the control animals (table 1).

TABLE 2. Hemodynamic Parameters, Splanchnic Blood Flow, and Oxygen Consumption during Isoflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.7%</th>
<th>1.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (min⁻¹)</strong></td>
<td>96 ± 3</td>
<td>91 ± 4</td>
<td>90 ± 4</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>105 ± 4</td>
<td>72 ± 3*</td>
<td>59 ± 3††</td>
</tr>
<tr>
<td><strong>CO (l·min⁻¹)</strong></td>
<td>4.1 ± 0.3</td>
<td>3.5 ± 0.2*</td>
<td>3.5 ± 0.3*</td>
</tr>
<tr>
<td><strong>SVR (dyn·sec·cm⁻⁵)</strong></td>
<td>2090 ± 136</td>
<td>1605 ± 71*‡</td>
<td>1405 ± 74**‡‡</td>
</tr>
<tr>
<td><strong>Syst. O₂C</strong></td>
<td>4.77 ± 0.35</td>
<td>4.38 ± 0.29*</td>
<td>4.06 ± 0.35*</td>
</tr>
<tr>
<td>(ml·min⁻¹·kg⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Q₅₀ (ml·min⁻¹·100 g⁻¹)</strong></td>
<td>112 ± 12</td>
<td>94 ± 10*</td>
<td>94 ± 13‡</td>
</tr>
<tr>
<td><strong>Splan O₂C</strong></td>
<td>0.97 ± 0.11</td>
<td>1.11 ± 0.12</td>
<td>1.22 ± 0.13</td>
</tr>
<tr>
<td>(ml·min⁻¹·kg⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>hep. ven. P₀₂ (mmHg)</strong></td>
<td>40 ± 1</td>
<td>35 ± 2*</td>
<td>31 ± 2††</td>
</tr>
<tr>
<td><strong>hep. art. R</strong></td>
<td>1.30 ± 0.27</td>
<td>0.62 ± 0.10</td>
<td>0.71 ± 0.17*</td>
</tr>
<tr>
<td>(mmHg·min·m⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>preportal R.</strong></td>
<td>159 ± 17</td>
<td>129 ± 13*</td>
<td>101 ± 11††</td>
</tr>
<tr>
<td><strong>hep. surf. P₀₂ 0-5 mmHg (%)</strong></td>
<td>8.4 ± 3.7</td>
<td>8.8 ± 3.7‡</td>
<td>20.3 ± 8.5††‡‡</td>
</tr>
<tr>
<td><strong>hep. surf. P₀₂ 0 mmHg (%)</strong></td>
<td>2.4 ± 1.2</td>
<td>2.8 ± 1.1</td>
<td>9.8 ± 3.6††‡‡</td>
</tr>
</tbody>
</table>

See table 1 for abbreviations.

* P < 0.05 vs. baseline before isoflurane.
‡ P < 0.05 vs. lower isoflurane concentration.
‡‡ P < 0.05 vs. corresponding time in the control group.
HEPATIC OXYGENATION WITH ISOFLURANE

Discussion

General Remarks

The present study was carried out in dogs during basal anesthesia produced by the long-acting narcotic piritramid, because surgical preparation required for the $pO_2$ determinations on the liver surface required anesthesia. Also, the use of an anesthetized preparation reduced stress-induced disturbances of hemodynamic data during sampling of baseline values that could not be excluded if these measurements were performed in awake animals. Finally, this experimental approach excluded influences when changing from spontaneous breathing to intermittent positive pressure ventilation on splanchnic flow parameters. The control group, which received no isoflurane, allowed assessment of the time dependent alterations in the preparations. In this group, all parameters remained stable over a 3-h observation period.

General influences on systemic hemodynamic parameters of isoflurane agree with data from the literature. When interpreting the results of this study, it has to be kept in mind that they do not necessarily solely represent the effects isoflurane inasmuch as anesthesia included the drugs given for induction as well as the continued infusion of piritramid. The combination of isoflurane with piri-
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METHODOLOGICAL REMARKS

Blood flow to the splanchnic organs was determined by radioactive microsphere method using a reference sample technique.\textsuperscript{14} Particles were injected into the left atrium to guarantee homogenous mixing with blood.\textsuperscript{21} Homogenous mixing was verified by comparing the left and right renal cortical flow values; as a routine in this laboratory, animals are excluded from studies when this flow difference exceeds 10%. In this study, there were no such exclusions. Mean diameter of the microspheres was

![Graphs showing summary histograms of hepatic surface \( p_{O_2} \) from six animals of the control group. Determinations were obtained in 1-h intervals. \( n \) denotes the total number of measurements, \( p_{aO_2} \) the mean arterial \( p_{O_2} \).](attachment:image)

![Graphs showing summary histograms of hepatic surface \( p_{O_2} \) from twelve animals during basic anesthesia with piritramid (baseline) and with 0.7 and 1.4 Vol% isoflurane. \( n \) indicates the total number of measurements. \( p_{aO_2} \) is the mean value of \( p_{O_2} \) in arterial blood during recording of the histograms. A leftward shift of the summary histograms and a concomitant increase of \( p_{O_2} \) values in the lowest \( p_{O_2} \) range can be observed with increasing concentrations of isoflurane.](attachment:image)

\textsuperscript{9} Cahalan MK, Lurz FW, Beaupre BN, Schwartz LA, Eger EI II: Narcotics alter the heart rate and blood pressure response to inhalation anesthetics (abstract). \textit{Anesthesiology} 59:A26, 1983.
HEPATIC OXYGENATION WITH ISOFLURANE

15 μm. With this size, systemic shunting is minimal, while
distribution of the streaming microspheres is still not
significantly different from red blood cells.22 We injected a
relatively large number of particles (2.5–4.0 millions) to
be sure that all tissue specimens contained at least 400
microspheres.21 This was also verified by dividing the
amount of radioactivity measured in the tissue samples
by the previously determined activity of a single micro-
sphere.

The major advantage of our technique of measuring
surface \( p_{O_2} \) is that it permits atraumatic measurement of
local tissue oxygenation (in contrast to needle electrodes
that may produce trauma and hemorrhage in the tissue,
thereby disturbing microcirculation). Additionally, the
covering teflon membranes of the surface electrodes avoid
contamination of the platinum wires by biologic material
that may be reduced by the voltage of the electrode. This
contamination of the electrode can alter the \( p_{O_2} \) deter-
minations and lead to a considerable electrode drift.
Certainly, the \( p_{O_2} \) measurements on the liver surface do not
necessarily reflect oxygen tensions in deeper layers of tis-
sue. The principle of this technique has, however, proved
useful in a variety of experimental approaches.13,15,17,18,23

The total weight of the electrode is less than 1.5 g,
thereby avoiding ischemia due to excessive pressure.
Control experiments have shown that the electrode can
be kept in place, without changing its position, for more
than 1 h without alterations of tissue oxygen pressures.
Pilot studies demonstrated that there is no influence of
oxygen from the ambient air, because, once the electrode
was placed on the surface of the liver, suffusion of the
area with pure oxygen or pure nitrogen had no effect.
Thus, any diffusion of \( O_2 \) from the lateral side into the
fluid-filled space between electrode and hepatic surface
can be excluded. This also indicates that there is no sig-
nificant influence of oxygen diffusing from room air into
small arterioles or precapillary vessels on the exposed sur-
face of the liver. Finally, correct contact of the electrode
with the hepatic tissue was verified after killing the animals
by iv potassium-chloride, where all wires recorded values
of 0 mmHg within a few minutes. It has been demon-
strated by Severinghaus et al.24 that halothane interferes
with \( p_{O_2} \) determinations. We have excluded this possibility
for isoflurane (as well as for enflurane) by equilibrating a
5 Vol.% oxygen calibration standard with different con-
centrations of the volatile anesthetics (0–5 Vol.%). Cor-
responding results have been reported by Seyde and
Longnecker.25

The hemispheric catchment area of a single wire of the
electrode (diameter about 50 μm) produces an averaged
oxygen tension measurement from a tissue volume in-
cluding several liver cells and their surrounding struc-
tures. Therefore, 80 to 100 \( p_{O_2} \) values on the surface of
the liver were determined in each animal at all three ex-
perimental stages to give a representative estimate of local
hepatic oxygenation.13,15,18 While the catchment area
of the surface electrode precludes determinations of \( p_{O_2} \) val-
ues within a single liver cell, the electrode does measure
cellular oxygen supply by measuring an averaged value of
cellular \( p_{O_2} \) and oxygen pressures in the surrounding
tissue. The histograms then give the net result of oxygen
supply, microcirculatory blood flow distribution, and the
metabolic demands of the tissue.18

Theoretical considerations28 and the range of the his-
tograms indicate a drop of \( p_{O_2} \) from the beginning of a
capillary to its end. The shape of the histogram is, there-
fore, determined by local microcirculatory patterns (e.g.,
capillary length, flow, distribution of flow) as well as me-
tabolic demand of the tissues. A low percentage of values
detectable different from 0 mmHg in the \( p_{O_2} \) histo-
grams of both groups under control conditions does not
necessarily indicate tissue damage.15,27 It is, however, ev-
dent that any attempt to evaluate the quality of tissue
oxygenation has to take the lower \( p_{O_2} \) values, in partic-
ular, into consideration. We, therefore, performed our
statistical analysis with such measuring points (i.e., lowest
histogram range 0–5 mmHg, and percentage of values
not different from 0 mmHg).

SPLANCHNIC BLOOD FLOW AND
OXYGEN CONSUMPTION

In this study, we have determined blood flow through
splanchnic organs, hepatic surface oxygen tensions, and
splanchnic oxygen consumption in 12 dogs during isoflu-
rane anesthesia. Two end-expiratory concentrations of
isoflurane (0.7 and 1.4 Vol.%) were studied. Baseline re-
cordings were obtained in the animals anesthetized with
the long-acting narcotic piritramid. To our knowledge,
there are no other data available concerning pure effects
of piritramid on the splanchnic circulation. Baseline values
of splanchnic oxygen consumption, blood flow, and he-
patic surface \( p_{O_2} \) agree with data from literature.7,8,13,15,28,29
Results of the control group \((n = 6)\), in which no isoflurane
was administered, were studied over a 3-h observation
period, indicating that there were no definite time varying
alterations.

The concentrations of isoflurane used correspond to
0.5 and 1.0 MAC, when isoflurane is the only anesthetic
administered.30 The iv anesthetics used for induction
of anesthesia and, particularly, the continued infusion of
the narcotic piritramid increase the total MAC equivalent
to an unknown extent that should be considered when in-
terpreting the results. A comparison with data from lit-
erature reveals that similar hemodynamic alterations were
observed at higher end-expired isoflurane concentra-
tions. In dogs in which no basic anesthetics were given
and only a small bolus of methohexital was injected at the

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beginning of the experiment, end-expiratory isoflurane concentrations of 2.8 Vol% were required to reduce MAP to 64 mmHg. In pigs, an end-tidal isoflurane concentration of 2.17 Vol% (corresponding to 1.5 MAC) reduced MAP to 69 mmHg. In our study, MAP was 59 mmHg when 1.4 Vol% were applied.

Because of the presumed difference in the MAC values, it seems justified to compare results not on the basis of anesthetic concentrations, but rather with regard to hemodynamic conditions under which they were obtained. Isoflurane at 0.7 and 1.4 Vol% reduced splanchnic blood flow in our animals to almost the same extent. At comparable mean arterial pressures of about 60 mmHg in dogs, portal blood flow values were almost identical in our study and in previous work (0.76 versus 0.74 ml·min⁻¹·g⁻¹). The percent change of splanchnic flow when MAP was reduced from about 100 to about 60 mmHg was identical (~16%). This demonstrates a quite similar pattern of vascular reactivity under both experimental approaches, which is not surprising, because the perfusion pressure dependence of splanchnic blood flow has been documented under a variety of experimental conditions. Also, in a porcine model, hepatic arterial flow remained unchanged from control values during isoflurane anesthesia. In these animals, blood flow through the entire gastro-intestinal tract showed a dose-dependent decrease that was less marked than the decrease of mean arterial pressure, but more closely related to cardiac output. This corresponds to our results, in which linear regression analysis revealed a significant correlation of cardiac output with splanchnic blood flow. Despite a reduced blood flow, isoflurane induced vasodilation in the preportal bed, since calculated vascular resistance decreased significantly at both concentrations confirming the results of Östman et al. Other studies have also shown isoflurane to be a mild preportal vasodilator if resistance is calculated on the basis of published data and similar results are reported for hepatic arterial tone. Thus, it appears appropriate to assume that isoflurane acts as a splanchnic vasodilator.

A decrease of hepatic venous \( pO_2 \) and a leftward shift of the \( pO_2 \) histograms were observed predominantly at the higher concentration of isoflurane. An increased number of 0 mmHg values in the surface \( pO_2 \) recordings was also detected. This indicates that, at least with the higher concentration of isoflurane, there was an increase in the percentage of hypoxic surface sites that shows an imbalance between hepatic oxygen supply and tissue metabolic demands. However, it appears that compensatory mechanisms in the hepatic microcirculation are sufficient to maintain tissue oxygenation during 0.7% isoflurane, since the significant deterioration of hepatic venous \( pO_2 \) is not followed by an alteration of tissue oxygenation. Reductions of hepatic venous \( pO_2 \) as an indicator of a deteriorated hepatic tissue oxygenation have also been documented for halothane and enflurane. A common finding of these investigations is that preportal, hepatic or, as in our study, splanchnic oxygen consumption remained unchanged, despite the well-accepted observation that these anesthetics reduce whole-body and some individual organ (e.g., brain, heart) oxygen consumptions. Furthermore, the splanchnic vascular bed is obviously unable, during application of these volatile anesthetics, to totally compensate the alteration of the oxygen supply to consumption ratio by an increase in blood flow. It is not possible to distinguish from the data presented whether the reduced hepatic tissue oxygenation in our experiments is due to an increased oxygen extraction in the preportal organs, hence a decreased oxygen supply, or if the increased oxygen extraction occurs in the liver itself. We purposely did not perform the laparotomy that would have been necessary for placing a catheter in the portal vein, because that procedure is known to alter hepatic perfusion. Data from literature obtained during halothane and enflurane support the first hypothesis. In contrast, results of studies of blood flow and oxygenation in the small intestine (which is the main contributor to portal flow) during isoflurane indicated a decreased oxygen consumption; this suggests, therefore, a higher portal venous \( pO_2 \) and a higher hepatic \( O_2 \) consumption as the source of the decreased hepatic surface \( pO_2 \). However, a recent in vitro study by Becker et al. indicates that there is no change in hepatic oxygen consumption produced by isoflurane, and Gelman et al. reported an unchanged portal venous oxygen content in miniature pigs treated with this anesthetic. The deterioration of hepatic tissue oxygenation, therefore, is probably predominantly the result of reduced portal flow, and hence a reduced oxygen supply through the portal vein.

In summary, anesthesia with isoflurane in this experimental model, particularly at 1.4 Vol%, resulted in a higher oxygen extraction of the total splanchnic bed. This was evidenced by the lower hepatic venous \( pO_2 \) and by a leftward shift of the hepatic \( pO_2 \) histograms with an increased number of low \( pO_2 \) values. A recent study by Gelman et al. suggested a better maintenance of total hepatic blood flow during isoflurane when compared to halothane. This finding might argue in favor of isoflurane. With respect to an altered oxygen supply-to-consumption ratio, qualitative differences do not seem to exist between the isoflurane data reported here and results from previous investigators of halothane or enflurane. It must be kept in mind that administration of the volatile anesthetics in all studies was associated with a reduction of splanchnic perfusion pressure, and that autoregulation in this area is not as intense as that in other organs. Although there was a significant reduction of resistance
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in the preportal organs of our animals, this effect was not sufficient to maintain blood flow. Thus, it cannot be excluded that the adverse effects of volatile anesthetics observed in this and in other studies may be absent if preportal blood flow remains constant.

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