Effect of Propofol Infusion on Splanchnic Hemodynamics and Liver Oxygen Consumption in the Rat
A Dose-Response Study

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Background: Propofol has been used for the maintenance of anesthesia. The effects of propofol infusion on splanchnic hemodynamics and liver oxygen consumption, however, have not been reported. In the current investigation, the authors studied the effects of a continuous infusion of propofol on systemic and splanchnic hemodynamics using a new method to measure liver oxygen consumption in awake control and anesthetized rats.

Methods: Cannulas were inserted into the left ventricle, femoral artery, portal vein, and hepatic vein during ether anesthesia, and the rats were allowed to awaken and recover for 3–4 h before study. Animals were infused for 30 min with either saline (controls) or propofol at a rate of 300, 600, 900, or 1,200 µg·kg⁻¹·min⁻¹. Cardiac output and organ blood flows were measured using radiolabelled microspheres, and blood samples from the femoral artery, portal vein, and hepatic vein were used to determine liver oxygen consumption.

Results: Mean arterial pressure decreased in a dose-dependent manner with a 25% reduction at the highest infusion rate. Systemic vascular resistance similarly decreased, whereas cardiac output remained unchanged at all the infusion rates. Hepatic arterial blood flow increased in a dose-dependent fashion over the dose range studied, to a maximum increase of 120%. Portal tributary blood flow increased by 30% at the highest infusion rate. Total liver blood flow increased in a dose-dependent manner to a maximum of 38%. Total oxygen delivery to the liver by the hepatic artery and portal vein increased in a dose-dependent fashion. Liver oxygen consumption increased in a dose-dependent fashion to a maximum increase of 51% at an infusion rate of 1,200 µg·kg⁻¹·min⁻¹. The percent of oxygen extracted by the liver was not altered by propofol infusion, and hepatic venous oxygen saturation did not decrease at any dose studied. Coronary and renal blood flows were not altered. Arterial PaO₂ increased from 31 ± 2 mmHg in awake control rats to 41 ± 2 mmHg in spontaneously breathing rats infused with 1,200 µg·kg⁻¹·min⁻¹ propofol.

Conclusions: The maintenance of anesthesia using an infusion of propofol resulted in an increase in liver oxygen consumption that was fully compensated for by an increase in oxygen delivery to the liver. Splanchnic hemodynamics and liver oxygenation are not adversely affected during maintenance of anesthesia with propofol in the normal rat. (Key words: Anesthesia, intravenous: propofol. Blood flow: hepatic artery; hepatic vein; portal vein. Liver oxygen consumption. Measurement technique: blood flow; microsphere.)

PROPOFOL, an intravenous anesthetic agent with a short duration of action, has proven effective both as an induction agent and for continuous intravenous maintenance of anesthesia. The short duration of action is explained by a very high total body clearance, caused primarily by hepatic clearance.¹,² Induction of anesthesia with propofol has been found to reduce cardiac output and arterial pressure, both in experimental animals and in humans. This reduction in cardiac output has been attributed to a decrease in systemic vascular resistance,³ a reduction in preload,⁴ and a negative inotropic effect.⁵,⁶ There have been few studies of the effect of propofol on splanchnic hemodynamics.¹,⁷ These authors, using an indicator dye clearance technique to monitor liver blood flow, reported a decrease in liver blood flow in

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Received from the Department of Anesthesia, Toronto Western Hospital and the Hospital for Sick Children, Toronto, Ontario, Canada; the Addiction Research Foundation, Toronto, Ontario, Canada; and the Departments of Anesthesia and Pharmacology, University of Toronto, Toronto, Ontario, Canada. Accepted for publication July 8, 1993. Supported by grants from The Medical Research Council of Canada.

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humans and sheep. Propofol, however, has been shown to inhibit the hepatic clearance of the indicator dye indocyanine green, raising a question as to the validity of these data.

The liver, in the presence of conditions that increase oxygen consumption or decrease oxygen supply, is known to be susceptible to hypoxic damage. It is, therefore, important to have a clear understanding of the effects of propofol on the splanchnic circulation. The current study in rats was undertaken to provide information on the effects of continuous intravascular administration of propofol using a recently developed method to measure liver blood flow and oxygen consumption in awake and unrestrained rats.

Materials and Methods

Male Sprague-Dawley rats, weighing 275–325 g, were studied with the approval of the University of Toronto Animal Care Committee. The animals were housed in a temperature- and humidity-controlled environment with a 12-h light/dark cycle. The rats fasted for 16 h with water ad libitum before study.

To determine liver oxygen consumption, canulas were inserted into the left ventricle, femoral artery, hepatic vein, and distal ileocolic vein (four-cannula group).

Cannulation of the Left Ventricle
During ether anesthesia, a 1-cm midline incision was made in the skin of the neck, and the right common carotid artery was exposed. A ligature was passed around the vessel, and a temporary clip was placed on the artery. A polyethylene cannula (Intermedic PE50, Clay Adams, Parsippany, NJ) was inserted into the vessel through a small incision proximal to the ligature, and was advanced into the left ventricle after releasing the clip. Localization of the cannula in the left ventricle was verified by monitoring the blood pressure waveform with a physiograph (Narco Biosystems, Houston, TX).

Cannulation of the Femoral Artery
A 1.5-cm skin incision was made over the right medial thigh, the femoral artery was isolated and temporarily occluded, and a ligature was passed around the vessel. The cannula was then passed up the artery through a small incision proximal to the ligature, and advanced to a position approximately 1 cm above the aortic bifurcation.

Cannulation of the Hepatic Vein
A laparotomy was performed through a 2.5-cm midline incision, and the median and left lateral lobes of the liver were located and separated to expose the hepatic vein. The hepatic vein was cannulated by direct puncture to a depth of approximately 1.5 mm. Free flow of blood into the cannula was confirmed using a syringe, before securing the cannula with glue (Histacryl blau; B. Braun Melsungen AG, Melsungen, Germany).

Cannulation of the Ileocolic Vein for Portal Venous Sampling
Through the laparotomy, a distal branch of the ileocolic vein was isolated by elevating the omentum. The ileocolic vein was cannulated by direct puncture, and the cannula was advanced up to the portal vein, a distance of about 0.5 cm. Free flow of blood was assessed using a syringe. This cannula sampled blood from the portal vein. The cannula was secured in place with glue, as described above.

The canulas were then tunneled subcutaneously, and were brought onto the skin surface of the mid back. The incisions were infiltrated with local anesthetic and sutured, and the rats were allowed to awaken and recover for 3–4 h, in standard 22 X 11 cm cages, before study. The total preparation of these animals required 20–25 min.

Experimental Design
After recovery from surgery, the animals were randomly allocated to receive an infusion of either saline (control) or propofol at a rate of 300, 600, 900, or 1,200 μg·kg⁻¹·min⁻¹, in a volume of 1 ml. After 30 min of infusion, cardiac output and organ blood flows were determined using radiolabeled microspheres, and blood samples were taken for oxygen content determination. Throughout these studies, ventilation was spontaneous.

To assess the effects of the laparotomy and the intrahepatic catheters on systemic and splanchnic hemodynamics, a separate group of rats was prepared with only the left ventricular and femoral arterial catheters (two-cannula group). Data from the two-cannula group were compared with those from the four-cannula group described above.

To assess the effects of mechanical ventilation on systemic and splanchnic hemodynamics, two additional groups of the rats infused with propofol at rates of 900 (900-V) and 1,200 (1,200-V) μg·kg⁻¹·min⁻¹ were...
studied. In these animals, the trachea was intubated, and the lungs were mechanically ventilated using a Harvard Small Animal Ventilator (Harvard Apparatus, Millis, MA), at a rate of 80–100 breaths/min and a tidal volume of 3.5 ml, for at least 10 min before hemodynamic studies.

**Cardiac Output and Organ Blood Flow Determination**

Cardiac output and organ blood flows were determined using radiolabeled microspheres (16.5 ± 0.1 μm diameter), as we previously described. The microspheres were mixed and diluted, and were drawn up into polyethylene tubing for counting before injection (model 1185; Nuclear Chicago, Chicago, IL). About 50,000 microspheres, labelled with either Co-57 or Sc-46 (New England Nuclear, Boston, MA), were infused into the left ventricle over a period of 20 s using an infusion pump. Starting 10 s before microsphere infusion, a reference sample was withdrawn from the femoral artery at a rate of 0.6 ml/min, for a period of 1 min. An equal volume of ficol (0.6 ml, 13% wt/vol; Sigma, St. Louis, MO), a nonionic synthetic polymer of sucrose, was infused through the microsphere tubing to replace the volume of blood sampled. After withdrawal of the reference sample, there was no radioactivity remaining in the circulation. The net counts injected were determined by subtraction of the count remaining in the polyethylene tubing from the counts obtained before injection into the left ventricle. Thereafter, blood samples were taken for oxygen content determination, the response to tail clamp was determined to assess anesthetic depth, and body temperature was measured, and the rats were killed using a bolus infusion of KCl into the left ventricle. The following organs were removed for radioactive counting: heart, lungs, kidneys, liver, spleen, stomach, and small and large intestine. The pancreas and omentum were isolated with the stomach and intestine.

Cardiac output, \( Q_t \) (ml·min⁻¹·kg⁻¹ body weight), was calculated as:

\[
Q_t = (C_i \cdot R) \cdot (C_r \cdot w)^{-1},
\]

where \( C_i = \) net counts injected; \( R = \) reference sample withdrawal rate; \( C_r = \) net counts in reference sample; and \( w = \) body weight (kg).

Organ blood flows, \( Q_o \) (ml·min⁻¹·kg⁻¹ body weight), were calculated as:

\[
Q_o = (Q_t \cdot C_o) \cdot (C_i)^{-1},
\]

where \( C_o = \) net counts in organ.

Hepatic arterial blood flow (HABF) was determined from the net counts within the liver. Portal tributary blood flow (PBF) was calculated as the sum of the blood flow to the spleen, stomach, omentum, pancreas, and small and large intestines.

Hepatic arterial vascular resistance (mmHg·ml⁻¹·min⁻¹·kg⁻¹), was calculated as mean arterial blood pressure divided by hepatic arterial blood flow. Preportal vascular resistance (mmHg·ml⁻¹·min⁻¹·kg⁻¹) was calculated as mean arterial blood pressure divided by portal tributary blood flow. Inferior vena caval and portal venous pressures were taken to be zero for these calculations.

**Oxygen Delivery, Uptake, and Extraction**

Blood samples for hemoglobin concentration and oxygen saturation were withdrawn from the femoral artery, hepatic vein, and portal vein (via the ileocolic catheter) immediately after blood flow studies. The blood samples, 0.2 ml each, were analyzed using an oximeter that measures both the hemoglobin concentration and the oxygen saturation (Radiometer OSM 2, Copenhagen, Denmark). Each blood sample was replaced with 3 volumes of normal saline.

Hepatic arterial oxygen delivery (DhaO₂, ml O₂·min⁻¹·kg⁻¹) was calculated as:

\[
DhaO₂ = HABF \cdot CaO₂,
\]

where \( CaO₂ = \) content of oxygen in arterial blood (ml O₂·ml⁻¹), calculated as % saturation \( \times \) 1.34 \( \times \) hemoglobin concentration.

Portal venous delivery of oxygen to the liver (DpvO₂, ml O₂·min⁻¹·kg⁻¹) was calculated as:

\[
DpvO₂ = PBF \cdot CpvO₂,
\]

where \( PBF = \) portal tributary blood flow and \( CpvO₂ = \) content of oxygen in portal venous blood (ml O₂·ml⁻¹), calculated as % saturation \( \times \) 1.34 \( \times \) hemoglobin concentration.

Total oxygen delivery to the liver (VtotO₂, ml O₂·min⁻¹·kg⁻¹), was calculated as:

\[
VtotO₂ = DhaO₂ + DpvO₂.
\]

Hepatic vein oxygen content (ChvO₂, ml O₂/ml), was calculated as:

\[
ChvO₂ = % \text{ saturation} \times 1.34 \times \text{hemoglobin concentration}.
\]
Oxygen consumption by the liver (\(\text{VI}_2\text{O}_2\), ml \(\text{O}_2\) · min\(^{-1}\) · kg\(^{-1}\)), was taken as the difference between total oxygen delivery and hepatic vein oxygen flow (\(\text{VhvO}_2\)), and was calculated as:

\[
\text{VI}_2\text{O}_2 = \text{DhaO}_2 + \text{DpvO}_2 - \text{VhvO}_2,
\]

where \(\text{VhvO}_2 = \text{ChvO}_2 \times \text{total liver blood flow}\).

Hepatic oxygen extraction (%) was calculated as:

\[
\% \text{ Extraction} = \frac{\text{VI}_2\text{O}_2 \cdot (\text{DhaO}_2 + \text{DpvO}_2)^{-1}}{100}.
\]

As with our previous studies, the animals showed no obvious evidence of being under stress after anesthesia for catheter insertion, and the prior anesthetic does not interfere with systemic or splanchnic hemodynamics in awake rats at the time of study.\(^{12-15}\) We have also shown that catheter insertion does not alter the hematocrit and, thus, there is no evidence for changes in circulating blood volume. Just before hemodynamic studies, the cannulas were connected for pressure monitoring and for the infusion and withdrawal of samples. This procedure did not appear to affect the animals. Hemodynamic and blood flow measurements in awake rats were carried out while the rats were freely mobile. During the experiments, heating lamps were used to maintain normothermia. Rectal temperatures at the end of the study were 37.2 ± 0.3°C.

Cardiac output, organ blood flow, vascular resistance, and oxygen consumption and delivery data were indexed to body weight (kg). Because the relationship of organ weight to body weight did not change throughout the study period, there were no differences in the conclusions derived when this form of expression was used as opposed to per gram organ weight.

The anesthetic potency of propofol infusion (ED50) was determined using the tail-clamp technique.\(^{19}\) Response to the tail clamp was assessed at the completion of the hemodynamic, blood flow, and oxygen consumption studies. A rubber-clad 6-inch hemostat clamped to the first ratchet position was applied to the mid portion of the tail. Gross purposeful movement of the head, limbs, or body was recorded as a positive response.\(^{19}\) The ED50 for propofol was determined using a Probit analysis of the proportion of animals responding to the stimulus.

Data are presented as means ± SEM. Data were analyzed with one-way and two-way ANOVA using SAS programming (Cary, NC). Comparison with control values and between infusion rates was done using the least significant difference method.\(^{19}\) The two- and four-cannula groups were compared using a two-way ANOVA.

Similarly, data from the spontaneously breathing and mechanically ventilated groups were compared using a two-way ANOVA. A linear regression analysis was used to assess dose-response relationships between the various blood flows and the infusion rates of propofol.

**Results**

**Effect of Propofol Infusion on Systemic Hemodynamics, Arterial Carbon Dioxide, and Response to Tail Clamp**

In the spontaneously breathing four-cannula rats, cardiac output and stroke volume were not affected by propofol infusion, with the exception of a 28% increase (\(P < 0.05\)) in cardiac output and a 24% increase (\(P < 0.05\)) in stroke volume at the 600-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) infusion rate (table 1). Mean arterial pressure and systemic vascular resistance were affected only at the 1,200-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) rate with decreases of 15% (\(P < 0.05\)) and 24% (\(P < 0.05\)), respectively.

To determine the hemodynamic effects of the laparotomy and the two intraperitoneal cannulas, a comparison was made between the two-cannula and four-cannula rats. The data from the two groups were comparable (tables 1 and 2). There were no differences between the control animals in either group. Cardiac output, mean arterial pressure, and systemic vascular resistance during propofol infusion were similar in both the two- and four-cannula groups. Likewise, arterial \(\text{P}_{\text{CO}_2}\), splanchnic blood flow, and blood flow to the lung, heart, and kidneys were similar in the two- and four-cannula groups (tables 1 and 2).

In ventilated rats, cardiac output and stroke volume were unchanged during propofol infusion, similar to findings in the spontaneously breathing rats (table 1). Mean arterial pressure decreased by 25% (\(P < 0.05\)) at both the 900-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) and 1,200-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) infusion rates (table 1). Systemic vascular resistance decreased by 30% (\(P < 0.05\)) at the 900-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) infusion rate and by 31% (\(P < 0.01\)) at the 1,200-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) infusion rate (table 1). These values, however, did not differ from those found in the spontaneously breathing animals.

Propofol infusion did not affect microsphere accumulation in the lung, with the exception of the 600-\(\mu\)g · kg\(^{-1}\) · min\(^{-1}\) infusion rate, indicating that this anesthetic drug does not affect systemic shunting (tables 1 and 2) under the conditions of the current study. Coronary arterial and renal blood flows were not af-
affected by the infusion of propofol at the rates studied (tables 1 and 2).

In the current study, \(P_{aCO_2}\) tension was 31 ± 2 mmHg in the awake control animals (table 1). This value was not significantly different in ventilated rats receiving propofol infusion or in the spontaneously breathing rats infused with propofol at 300 \(\mu g \cdot kg^{-1} \cdot min^{-1}\). There was, however, a significant increase in \(P_{aCO_2}\) in the spontaneous breathing rats infused with propofol at 600, 900, and 1,200 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) (table 1). None of the rats, either breathing spontaneously or ventilated, became hypoxic with \(P_{aCO_2}\) values ranging from 107 ± 4 mmHg in the control animals to 91 ± 6 mmHg at the 1,200-\(\mu g \cdot kg^{-1} \cdot min^{-1}\) infusion rate.

In assessing the anesthetic effect of infused propofol, all rats reacted purposefully to the tail clamp at the 300-\(\mu g \cdot kg^{-1} \cdot min^{-1}\) dose, while 71% responded at the 600-\(\mu g \cdot kg^{-1} \cdot min^{-1}\) dose, and none responded to tail clamp at either the 900 or the 1,200-\(\mu g \cdot kg^{-1} \cdot min^{-1}\) infusion rate. This gave a calculated ED50 value for propofol infusion in rats of approximately 650 \(\mu g \cdot kg^{-1} \cdot min^{-1}\).

**Effect of Propofol Infusion on Splanchic Hemodynamics**

Basal hepatic arterial blood flows were 10.5 ± 1.9 and 10.9 ± 0.8 ml \cdot min^{-1} \cdot kg^{-1} in the four-cannula and two-cannula awake control groups, respectively (tables 3 and 4). In the four-cannula group, there was a dose-dependent increase in hepatic arterial blood flow with increasing doses of propofol (\(F = 7.91; P < 0.01\)). Hepatic arterial blood flow increased by approximate 100% at the 1,200-\(\mu g \cdot kg^{-1} \cdot min^{-1}\) infusion rate (table 3). Hepatic arterial vascular resistance decreased in a dose-dependent manner (\(F = 17.76; P < 0.001\)) (table 3). Similar dose-dependent changes were observed for hepatic arterial blood flow and vascular resistance in the animals implanted with two cannulas (table 4), as well as in mechanically ventilated animals (tables 3 and 4).

Basal portal tributary blood flows were 34.8 ± 1.6 and 38.9 ± 2.3 ml \cdot min^{-1} \cdot kg^{-1} in the four-cannula and two-cannula awake control groups, respectively (tables 3 and 4). There was an increase in portal tributary blood flow during propofol administration in the spontaneously breathing four-cannula rats at infusion rates of 600, 900, and 1,200 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) (table 3). This was associated with a dose-dependent decrease in preportal vascular resistance (\(F = 8.05; P < 0.01\)) (table 3). The increase in small intestinal blood flow with increasing infusion rates of propofol (table 3) accounted for the major proportion of the increase in portal tributary blood flow. In the two-cannula group, small intestinal and portal tributary blood

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Table 1. Effect of Propofol Infusion on Systemic Hemodynamics in Rats with 4-Cannulas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>300</th>
<th>600</th>
<th>900-s</th>
<th>900-v</th>
<th>1,200-s</th>
<th>1,200-v</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (mg \cdot m^{-1} \cdot kg^{-1})</td>
<td>222 ± 9</td>
<td>243 ± 16</td>
<td>286 ± 15</td>
<td>247 ± 21</td>
<td>232 ± 15</td>
<td>238 ± 7</td>
<td>241 ± 9</td>
</tr>
<tr>
<td>Stroke volume (ml \cdot kg^{-1})</td>
<td>0.58 ± 0.04</td>
<td>0.63 ± 0.05</td>
<td>0.73 ± 0.04*</td>
<td>0.71 ± 0.09</td>
<td>0.89 ± 0.02</td>
<td>0.86 ± 0.03</td>
<td>0.60 ± 0.05</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93 ± 5</td>
<td>86 ± 5</td>
<td>95 ± 3</td>
<td>80 ± 6</td>
<td>70 ± 7*</td>
<td>76 ± 6*</td>
<td>70 ± 10†</td>
</tr>
<tr>
<td>SVR (mmHg \cdot ml^{-1} \cdot min^{-1} \cdot kg^{-1})</td>
<td>0.42 ± 0.03</td>
<td>0.36 ± 0.03</td>
<td>0.34 ± 0.03</td>
<td>0.34 ± 0.05</td>
<td>0.30 ± 0.04*</td>
<td>0.32 ± 0.03*</td>
<td>0.29 ± 0.04†</td>
</tr>
<tr>
<td>Lung blood flow (ml \cdot m^{-1} \cdot kg^{-1})</td>
<td>2.7 ± 0.5</td>
<td>4.4 ± 0.6</td>
<td>6.7 ± 0.9*</td>
<td>4.0 ± 0.7</td>
<td>3.9 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>Coronal blood flow (ml \cdot m^{-1} \cdot kg^{-1})</td>
<td>16.5 ± 1.9</td>
<td>14.0 ± 0.8</td>
<td>12.8 ± 2.9</td>
<td>16.0 ± 3.9</td>
<td>10.5 ± 0.9</td>
<td>14.2 ± 2.2</td>
<td>16.9 ± 3.2</td>
</tr>
<tr>
<td>Renal blood flow (ml \cdot m^{-1} \cdot kg^{-1})</td>
<td>37.9 ± 3.2</td>
<td>47.9 ± 3.9</td>
<td>49.0 ± 4.6*</td>
<td>44.8 ± 2.3</td>
<td>38.7 ± 2.7</td>
<td>36.6 ± 2.1</td>
<td>38.5 ± 4.5</td>
</tr>
<tr>
<td>(P_{aCO_2}) (mmHg)</td>
<td>31 ± 2</td>
<td>31 ± 2</td>
<td>39 ± 3‡</td>
<td>40 ± 3‡</td>
<td>30 ± 1</td>
<td>41 ± 2†</td>
<td>30 ± 1</td>
</tr>
<tr>
<td>(P_{aO_2}) (mmHg)</td>
<td>107 ± 4</td>
<td>99 ± 5</td>
<td>108 ± 10</td>
<td>99 ± 3</td>
<td>91 ± 6</td>
<td>102 ± 9</td>
<td>92 ± 7</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

s = spontaneously breathing rats; v = ventilated rats; MAP = mean arterial pressure; SVR = systemic vascular resistance.

* \(P < 0.05\) versus awake control rats.

† \(P < 0.01\) versus awake control rats.

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Table 2. Effect of Propofol Infusion on Systemic Hemodynamics in Rats with 2-Cannulas

<table>
<thead>
<tr>
<th>Number:</th>
<th>Control</th>
<th>900-s</th>
<th>1,200-s</th>
<th>1,200-v</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (ml·m⁻¹·kg⁻¹)</td>
<td>231 ± 14</td>
<td>271 ± 16</td>
<td>265 ± 21</td>
<td>264 ± 14</td>
</tr>
<tr>
<td>Stroke volume (ml·kg⁻¹)</td>
<td>0.59 ± 0.04</td>
<td>0.66 ± 0.07</td>
<td>0.71 ± 0.05</td>
<td>0.66 ± 0.07</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92 ± 5</td>
<td>83 ± 8</td>
<td>100 ± 2</td>
<td>77 ± 6*</td>
</tr>
<tr>
<td>SVR (mmHg·ml⁻¹·min⁻¹·kg⁻1)</td>
<td>0.41 ± 0.03</td>
<td>0.35 ± 0.03</td>
<td>0.37 ± 0.02</td>
<td>0.29 ± 0.02↑</td>
</tr>
<tr>
<td>Lung blood flow (ml·m⁻¹·kg⁻¹)</td>
<td>2.7 ± 0.5</td>
<td>4.3 ± 0.7</td>
<td>4.2 ± 0.7</td>
<td>5.2 ± 1.4</td>
</tr>
<tr>
<td>Coronary blood flow (ml·m⁻¹·kg⁻¹)</td>
<td>15.4 ± 3.9</td>
<td>14.3 ± 1.9</td>
<td>16.0 ± 2.9</td>
<td>14.0 ± 3.3</td>
</tr>
<tr>
<td>Renal blood flow (ml·m⁻¹·kg⁻¹)</td>
<td>39.3 ± 4.4</td>
<td>44.3 ± 2.4</td>
<td>44.5 ± 4.5</td>
<td>39.8 ± 3.8</td>
</tr>
<tr>
<td>P&lt;sub&gt;aco2&lt;/sub&gt; (mmHg)</td>
<td>29 ± 1</td>
<td>31 ± 1</td>
<td>39 ± 2↑</td>
<td>34 ± 1</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

s = spontaneously breathing rats; v = ventilated rats; MAP = mean arterial pressure; SVR = systemic vascular resistance.

* P < 0.05 versus awake control rats.

↑ P < 0.01 versus awake control rats.

flow and preportal vascular resistance did not change significantly (table 4).

There was a dose-dependent increase in total liver blood flow (F = 8.99; P < 0.005) with increasing infusion rates of propofol in the four-cannula group (table 3). In the two-cannula animals, total liver blood flow increased by 39% (P < 0.01) and by 32% (P < 0.05) in the 1,200-s and 1,200-v groups, respectively (table 4). There was no difference in portal tributary or total liver blood flow between the spontaneously breathing and mechanically ventilated animals (tables 3 and 4).

Effect of Propofol Infusion on Splanchnic Oxygenation

Oxygen delivery to the liver via the hepatic artery increased by 98% (P < 0.05) at the 1,200 µg·kg⁻¹·min⁻¹ infusion rate in ventilated animals (table 5). Oxygen delivery via the portal vein did not change with propofol infusion (table 5). Total oxygen delivery to the liver increased in a dose-dependent fashion during propofol infusion (F = 5.65; P < 0.02), from a control value of 5.67 ± 0.32 ml O₂·min⁻¹·kg⁻¹, to a value of 7.78 ml O₂·min⁻¹·kg⁻¹ in the 1,200-v group (table 5).

Table 3. Effect of Propofol Infusion on Splanchnic Hemodynamics in Rats with 4-Cannulas

<table>
<thead>
<tr>
<th>Number:</th>
<th>Control</th>
<th>300</th>
<th>600</th>
<th>900-s</th>
<th>900-v</th>
<th>1,200-s</th>
<th>1,200-v</th>
</tr>
</thead>
<tbody>
<tr>
<td>HABF</td>
<td>10.5 ± 1.9</td>
<td>12.2 ± 1.6</td>
<td>16.7 ± 1.9*</td>
<td>15.8 ± 1.4</td>
<td>18.1 ± 1.7↑</td>
<td>16.1 ± 3.5*</td>
<td>22.0 ± 2.2↑</td>
</tr>
<tr>
<td>HAVR</td>
<td>10.1 ± 1.1</td>
<td>7.8 ± 1.3</td>
<td>6.4 ± 1.0↑</td>
<td>5.2 ± 0.5↑</td>
<td>5.9 ± 0.8↑</td>
<td>5.2 ± 0.7↑</td>
<td>4.5 ± 0.7↑</td>
</tr>
<tr>
<td>PBF</td>
<td>34.8 ± 1.6</td>
<td>42.8 ± 1.5</td>
<td>47.4 ± 3.2↑</td>
<td>50.1 ± 4.5↑</td>
<td>43.0 ± 4.2</td>
<td>45.5 ± 4.2↑</td>
<td>44.1 ± 2.8↑</td>
</tr>
<tr>
<td>PpVR</td>
<td>2.60 ± 0.12</td>
<td>2.01 ± 0.09</td>
<td>2.05 ± 0.16</td>
<td>1.62 ± 0.13↑</td>
<td>2.48 ± 0.29</td>
<td>1.83 ± 0.24↑</td>
<td>1.85 ± 0.21↑</td>
</tr>
<tr>
<td>Spleen</td>
<td>4.0 ± 0.3</td>
<td>5.5 ± 0.7</td>
<td>4.9 ± 0.8</td>
<td>5.0 ± 0.7</td>
<td>3.8 ± 0.7</td>
<td>3.9 ± 0.8</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>Gastric</td>
<td>2.8 ± 0.2</td>
<td>3.8 ± 0.2</td>
<td>5.0 ± 0.7</td>
<td>4.9 ± 0.8</td>
<td>3.1 ± 0.5</td>
<td>4.1 ± 0.7</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td>Small intestine</td>
<td>20.3 ± 1.0</td>
<td>26.4 ± 1.7</td>
<td>25.4 ± 1.7*</td>
<td>28.9 ± 3.2↑</td>
<td>26.9 ± 2.7*</td>
<td>20.8 ± 2.5*</td>
<td>27.0 ± 1.6*</td>
</tr>
<tr>
<td>Large intestine</td>
<td>8.1 ± 0.8</td>
<td>8.6 ± 0.8</td>
<td>12.1 ± 0.9</td>
<td>10.3 ± 0.9</td>
<td>9.1 ± 0.9</td>
<td>10.1 ± 1.2</td>
<td>10.1 ± 1.1</td>
</tr>
<tr>
<td>Total hepatic</td>
<td>47.9 ± 1.9</td>
<td>55.0 ± 2.1</td>
<td>64.2 ± 3.6↑</td>
<td>66.0 ± 5.6↑</td>
<td>61.1 ± 5.8↑</td>
<td>61.8 ± 4.9↑</td>
<td>66.1 ± 5.2↑</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

s = spontaneously breathing rats; v = mechanically ventilated rats; HABF = hepatic arterial blood flow (ml·min⁻¹·kg⁻¹); HAVR = hepatic arterial vasoreaction (mmHg·ml⁻¹·min⁻¹·kg⁻¹); PBF = portal tributary blood flow (ml·min⁻¹·kg⁻¹); PpVR = portal preportal vascular resistance (mmHg·ml⁻¹·min⁻¹·kg⁻¹).

* P < 0.05 versus awake control rats.

↑ P < 0.01 versus awake control rats.

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Hepatic vein oxygen saturation during propofol infusion did not differ from the awake control values (Table 5). Oxygen extraction by the liver was not affected by propofol infusion (Table 5).

Oxygen consumption by the liver increased in a dose-dependent manner during propofol infusion (F = 6.89; P < 0.01), from a control value of 3.15 ± 0.25 ml O₂ min⁻¹·kg⁻¹ to a value of 4.77 ± 0.47 (P < 0.01) ml O₂ min⁻¹·kg⁻¹ in the 1,200-v group (Table 5).

**Discussion**

The current study establishes, for the first time, a methodology for measuring hepatic oxygen consumption in awake and unrestrained rats. The determination of systemic and splanchnic hemodynamics by the microsphere method requires placement of cannulas in the left ventricle for microsphere injection, and in the femoral artery for reference sample withdrawal. To measure liver oxygen consumption, two additional cannulas are required to sample blood for oxygen content across the liver. This was achieved by placing catheters into the hepatic vein and into a distal bifurcation of the ileocolic vein. This latter cannula was advanced toward the porta hepatis to sample blood and determine oxygen content in the portal vein. This technique provides a method for taking multiple samples across the liver, and could be used not only for oxygen consumption determination, but also for the determination of the clearance of substances by the liver. Also, this method for liver blood flow determination is not influenced by the presence of propofol, as has been shown for the indicator dye technique.¹

A number of aspects of the study design are important. First, a single species and strain was used throughout the study. Awake, unsedated, unanesthetized controls were used to obtain basal values that were unaffected by the presence of other drugs. Previous studies of liver oxygen consumption in the rat have used anesthetized animals.²⁻⁰ A well-established method, using microspheres, was used to determine blood flow to the liver and to the individual organs that contribute to portal venous blood flow.¹²⁻¹⁵,¹⁷⁻²³,²² The dose-response effects for propofol were established using a dose range that encompassed the ED₅₀ for continuous infusion of this anesthetic agent. It is of interest that the two additional intraperitoneal cannulas did not significantly alter basal liver blood flow when compared with rats in which only the left ventricle and femoral artery were cannulated. Likewise, the blood flow data during propofol infusion in rats with four cannulas were virtually identical to those in the animals with two cannulas, further indicating that the two intraperitoneal catheters did not significantly alter splanchnic hemodynamics under the conditions of the current study.

In the current study, the systemic hemodynamic responses to propofol were similar to those reported previously. In agreement with studies in sheep,⁷ dogs,¹⁴,²⁴ and humans,⁵ no reduction in cardiac output was ob-

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* Data are mean ± SEM.

s = spontaneously breathing rats; v = mechanically ventilated rats; HABF = hepatic arterial blood flow (ml·min⁻¹·kg⁻¹); HAVR = hepatic arterial vascular resistance (mmHg·mL⁻¹·min⁻¹·kg⁻¹); PBF = portal blood flow (ml·min⁻¹·kg⁻¹); PpVR = portal venous vascular resistance (mmHg·mL⁻¹·min⁻¹·kg⁻¹).

* P < 0.01 versus awake control rats.

† P < 0.05 versus awake control rats.
Table 5. Effect of Propofol Infusion on Hepatic Oxygen Delivery and Consumption

<table>
<thead>
<tr>
<th>Propofol Infusion (µg·kg⁻¹·m⁻³)</th>
<th>Oxygen Delivery (ml·m⁻¹·kg⁻¹)</th>
<th>Hepatic Ven O₂ Saturation (%)</th>
<th>Liver Oxygen Consumption (ml·m⁻¹·kg⁻¹)</th>
<th>Extraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 10)</td>
<td>DhhO₂ = 1.93 ± 0.39</td>
<td>3.83 ± 0.31</td>
<td>5.76 ± 0.32</td>
<td>30.7 ± 2.6</td>
</tr>
<tr>
<td>300 (n = 5)</td>
<td>DppO₂ = 1.89 ± 0.32</td>
<td>4.68 ± 0.33</td>
<td>6.57 ± 0.46</td>
<td>29.8 ± 1.4</td>
</tr>
<tr>
<td>600 (n = 7)</td>
<td></td>
<td>5.45 ± 0.47*</td>
<td>8.11 ± 0.51†</td>
<td>32.4 ± 2.3</td>
</tr>
<tr>
<td>900-s (n = 6)</td>
<td></td>
<td>4.31 ± 0.57</td>
<td>6.72 ± 0.67</td>
<td>33.8 ± 2.5</td>
</tr>
<tr>
<td>900-v (n = 7)</td>
<td></td>
<td>4.38 ± 0.63</td>
<td>7.23 ± 0.69</td>
<td>26.5 ± 2.3</td>
</tr>
<tr>
<td>1,200-s (n = 11)</td>
<td></td>
<td>4.67 ± 0.61</td>
<td>7.26 ± 0.63*</td>
<td>27.7 ± 2.3</td>
</tr>
<tr>
<td>1,200-v (n = 7)</td>
<td></td>
<td>4.01 ± 0.50</td>
<td>7.78 ± 0.68*</td>
<td>22.8 ± 2.4</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

DhhO₂ = delivery of oxygen via hepatic artery; DppO₂ = delivery of oxygen via portal vein; total = total liver oxygen delivery; extraction = extraction of oxygen by the liver; s = spontaneously breathing rats; v = mechanically ventilated rats.

* P < 0.05 versus awake control rats.
† P < 0.01 versus awake control rats.

served in response to the continuous infusion of propofol. This contrasts with the reduction in cardiac output observed after a bolus induction dose of propofol in humans⁴ and dogs.⁵ The dose-dependent reduction in mean arterial pressure and systemic vascular resistance is also consistent with these previous reports. In the current study, the lack of an increase in stroke volume in the face of a reduction in afterload indicates that myocardial contractility was also decreased. Under the conditions of this study, however, the systemic hemodynamic effects during maintenance of anesthesia with propofol as the sole anesthetic agent would appear to be small. Indeed, there was no effect on renal blood flow or coronary blood flow over the dose range used.

Effect of Propofol Infusion on Splanchnic Hemodynamics

In the current study, the infusion of propofol resulted in an increase in total liver blood flow. This increase was a result of an increase in both hepatic arterial and portal tributary blood flow. There was a marked reduction in the vascular resistances in these territories, indicating that propofol has a pronounced vasodilator effect on the splanchnic circulation. The splanchnic hemodynamic responses to propofol observed in the four-cannula and two-cannula animals were similar, with the exception of the portal tributary blood flow, which was slightly greater in the two-cannula control animals. This difference may represent the well known effects of a laparotomy on the splanchnic circulation.²³

In the current study, splanchnic blood flow appeared to be independent of circulating carbon dioxide tension. The changes in carbon dioxide tensions observed in the current study are small relative to those previously shown to influence the splanchnic circulation.²⁶

The current studies are in contrast to previous work in humans and sheep using an indicator dye method to estimate the effects of propofol on liver blood flow.¹⁷ These prior studies found a reduction in liver blood flow after induction with propofol, and a return to control values during maintenance. The reason for this discrepancy is not immediately obvious; however, it may relate to the different methods used in the studies. Propofol has been shown to have profound effects on the hepatic clearance of the indicator dye indocyanine green, an effect that probably also applies to the dye bromosulphalein.⁷ In addition, the latter dye has significant nonhepatic clearance and enterohepatic recirculation,²⁷,²⁸ and, thus, may also not give a true indication of liver blood flow changes during propofol administration. The use of microspheres in the current study has been well documented to give accurate estimates of liver blood flow, as well as allowing for the separate determination of hepatic arterial and portal tributary blood flow.¹¹,²⁵

In the current study, propofol infusion resulted in a modest increase in liver oxygen consumption. This is in contrast to studies in humans in which total splanchnic oxygen consumption was found to be unchanged after the induction and the maintenance of anesthesia with propofol.¹ The increase in liver oxygen demand in the current study appeared to be fully compensated by an increased supply of oxygen delivery to the liver. This conclusion was supported by the lack of a reduc-

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tion in hepatic vein oxygen saturation, and indicates that the liver does not become hypoxic during propofol infusion. The reason for the increase in oxygen consumption by the liver is not known, but may reflect an increase in hepatic metabolic activity during the clearance of propofol or, perhaps, metabolism of the emulsion of soybean oil, glycerol, and egg phosphatide used to suspend the propofol. Under specific in vitro conditions, other anesthetic agents have been found to increase liver oxygen consumption. Likewise, an increase in liver oxygen consumption has been demonstrated after the administration of lipids. The current results are similar to those reported in dogs for sevoflurane, halothane, enflurane, and isoflurane, in which liver oxygenation was also maintained during anesthesia with these inhalational agents. These findings are also consistent with studies in pigs that showed a small left shift in liver surface oxygen $P_{O_2}$ histograms without evidence of liver hypoxia during anesthesia with isoflurane and enflurane. The infusion of the intravenous anesthetics thiopental, athesin, and etomidate in dogs was found to reduce oxygen delivery to the liver. Although hepatic vein oxygen content was reduced, liver oxygen consumption remained constant during maintenance of anesthesia with these agents.

In conclusion, propofol infusion at rates resulting in surgical levels of anesthesia is accompanied by an increase in hepatic oxygen consumption that is fully compensated for by an increase in oxygen delivery to the liver. Maintenance infusions of propofol in rats do not appear to adversely affect the splanchnic circulation.

References


27. Leeve CM, Bender J, Silverberg M, Naylor J: Physiology of dye extraction by the liver: Comparative studies of sulphobromophthalein and indocyanine green. Ann N Y Acad Sci 111:161–175, 1963


