Hepatic Circulation during Sodium Nitroprusside Infusion in the Dog

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Changes in the hepatic circulation and oxygen supply during sodium nitroprusside (SNP) infusion were studied in 14 dogs anesthetized with pentobarbital, 30 mg/kg. Portal and hepatic arterial blood flows were measured with electromagnetic flowmeters. Aortic, portal and hepatic vein pressures were recorded, and pH, PCO₂, O₂ content, and lactate and pyruvate concentrations of blood from these vessels were measured. Cardiac output was determined by thermodilution using a Swan-Ganz catheter. In half the dogs a surgical preparation permitted controlled portal blood flow. SNP, 3–5 μg/kg/min, decreased mean arterial blood pressure as much as 15 per cent with no significant change in hepatic circulation. Doses of 10–20 μg/kg/min decreased arterial blood pressure 40 per cent, portal pressure 44 per cent, and portal blood flow 25 per cent. Hepatic arterial blood flow increased 13 per cent. There was no significant change in oxygen content of arterial, portal or hepatic vein blood, in oxygen consumption of the liver, or in the ratio of lactate to pyruvate produced by the liver. Concentrations of more than 25 μg/kg/min decreased arterial blood pressure more than 50 per cent from control level, decreased portal and hepatic arterial blood flows as much as 80 and 40 per cent, respectively, and decreased oxygen content of portal and hepatic vein blood as much as 5 ml oxygen/100 ml blood. In conditions of steady portal blood flow infusion of SNP led to a decrease in portal pressure by 18 per cent and a decrease in hepatic arterial blood flow. It is concluded that SNP in concentrations that decrease systemic blood pressure as much as 40 per cent of the baseline value does not lead to hepatic hypoxia in normal dogs. SNP decreases portal presinusoidal resistance and does not interfere with the ability of the liver to increase hepatic arterial blood flow in conditions of insufficient portal circulation. (Key words: Liver; blood flow; oxygen consumption. Anesthetic techniques: hypotension, induced, nitroprusside.)

The influence of sodium nitroprusside (SNP) on systemic circulation has been thoroughly investigated,1–3 but changes in hepatic circulation caused by SNP are still not known.2 The only study in this area did not show significant changes in total hepatic blood flow.4 However, the specific changes in portal blood flow and hepatic arterial blood flow during SNP administration, and the effect on hepatic autoregulation, are not known. The intent of this study was to measure the changes in hepatic circulation and oxygen supply during SNP infusion.

Methods

Fourteen dogs of both sexes ranging in body weight from 15 to 30 kg were used in these experiments. Anesthesia was induced by an intravenous injection of sodium pentobarbital, 30 mg/kg, and supplemented during the experiment as needed. The dogs were allowed to breathe spontaneously through an endotracheal tube. A polyethylene catheter was inserted into the aorta via a femoral artery and a Swan-Ganz catheter was introduced into the pulmonary artery for cardiac output measurement by thermodilution. The dogs' temperatures were maintained in a normal range by a heat lamp. The dogs were divided into two groups of seven each.

Group I

A catheter was inserted into a hepatic vein via the right jugular vein under fluoroscopic control. After laparotomy a polyethylene catheter was introduced into the portal vein through a branch of the superior mesenteric vein. The portal vein and common hepatic artery were exposed for placement of electromagnetic flow probes and the gastroduodenal artery was ligated to assure that all blood flowing through the hepatic artery entered the liver. Portal and hepatic arterial blood flows were measured with a two-channel electromagnetic flowmeter (model Narco RT-500), accompanied by the proper-sized probe for each vessel.

During experiments all catheters were connected to Statham P23 pressure transducers. Pressures in the aorta, pulmonary artery, and portal and hepatic veins were continuously recorded on a Gould 2600 recorder. Hepatic arteriolar resistance and portal venular resistance were calculated (see Appendix).

Arterial and portal and hepatic vein blood samples were taken periodically for determination of pH, PCO₂, and P O₂ values (Radiometer pH-27 meter and gas monitor type PHA 9276). Oxygen saturation and oxyhemoglobin were measured directly by an IL-182 CO-oximeter. Lactate and pyruvate concentrations were determined spectrophotometrically in samples.
of arterial and portal and hepatic vein blood. Oxygen content in blood samples, hepatic oxygen consumption, and ratio of lactate to pyruvate produced by the liver were calculated (see Appendix). SNP was infused by a Harvard infusion pump in concentrations ranging from 3 to 30 μg/kg/min during 20 to 50 min to observe a full range of response. Each dog received one to three infusions. Total doses of SNP did not exceed 1.5 mg/kg, to prevent cyanide toxicity.4

**Group II**

This group of dogs was used to measure the same variables during conditions of steady portal blood flow. Following administration of heparin, 1.5–2 mg/kg, intravenously, the portal vein was transected and polyethylene bypasses were inserted into the intestinal and hepatic ends of the portal vein. The blood from the intestinal end of the portal vein was directed to an exposed jugular vein. Arterial blood from the aorta was pumped into the hepatic end of the portal vein by a roller pump (300–400 ml/min) via a large catheter, previously inserted through a femoral artery. This preparation provided steady portal blood flow and allowed the observed changes in hepatic arterial blood flow and portal pressure to be independent of changes in portal blood flow. In these experiments portal pressure was measured through the tube inserted into the hepatic end of portal vein, and hepatic-vein pressure was measured at the junction of the hepatic veins and the inferior vena cava through a catheter inserted into the inferior caval vein via a femoral vein.

Nitroprusside, 5–10 μg/kg/min, was infused by a Harvard infusion pump into the portal or systemic veins. In the first group of experiments the main goal was to observe changes in the hepatic circulation in response to different concentrations of SNP, while in the second group 5–10 μg/kg/min were sufficient to produce those circulatory effects that facilitated our studies of the mechanism of SNP effects on hepatic circulation. This concentration was infused into the portal vein during temporary (8–10 min) occlusion of the hepatic artery six times. After each experiment the dog was sacrificed, the liver was weighed, and flows were calculated in ml/min/100 g of the liver.

Using the standard error of the mean, correlation analysis was computed for all data. The results obtained during successive phases of the experiment were compared using t tests for paired data. The Hewlett-Packard 9815A calculator with its statistical program package was used for all regression calculations and statistical tests. All plotting was done on a Tektronix 4602 Digital Plotter controlled by a HP 9815A calculator.

**Results**

**Group I**

Nitroprusside, 3–5 μg/kg/min, caused a decrease in mean arterial pressure of as much as 15 per cent and no significant change in hepatic circulation. Concentrations of more than 25 μg/kg/min decreased arterial blood pressure more than 50 per cent of control, together with considerable and significant decreases in portal and hepatic arterial blood flows of as much as 80 and 40 per cent, respectively and in O₂ content in the blood of portal and hepatic veins of as much as 5 ml O₂/100 ml blood. Thus, 3–5 μg/kg/min did not produce sufficient hemodynamic changes, whereas more than 25 μg/kg/min produced excessive hemodynamic changes. Both of these groups of data were eliminated. The rest of the data (10–20 μg/kg/min) are analyzed and presented below.

Nitroprusside, 10–20 μg/kg/min, caused a maximum decrease in mean arterial blood pressure by 40 per cent at the twentieth minute (table 1). At the same time, portal pressure had decreased 44 per cent and portal blood flow 25 per cent. The decrease in portal pressure was initially seen at the second minute of the infusion during conditions of a slight temporary increase in portal blood flow (table 1). Hepatic arterial blood flow increased in 13 observations and decreased in three.

Changes in O₂ content in arterial, portal and hepatic vein blood, in hepatic O₂ consumption, and in the ratio of lactate to pyruvate produced by the liver were not significant. After 20 to 30 minutes of SNP infusion, a slight tendency of hepatic circulatory variables to return towards baseline values was observed.

**Group II**

Intraportal SNP infusion led to a significant decrease in portal pressure in conditions of steady portal blood flow (supported by pump), regardless of whether or not the hepatic artery was occluded (table 2). Hepatic arterial blood flow was observed to decrease during intraportal as well as intravenous SNP infusion. This decrease was related to a decrease in arterial blood pressure (fig. 1).

**Discussion**

The observed initial temporary increase in portal blood flow during SNP infusion must be associated with a decrease in splanchnic vascular resistance. The later consistent decreases in portal blood flow might be related to the decreases in arterial blood pressure and cardiac output. An eventual increase in blood catecholamine or renin levels during SNP infusion was
Table 1. Average Changes (± SE) in Hepatic Circulation during Infusion of Sodium Nitroprusside (SNP), 10–20 μg/kg/Min (Group 1)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Baseline Value</th>
<th>2nd Min</th>
<th>5th Min</th>
<th>15th Min</th>
<th>20th Min</th>
<th>30th Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_{a} (torr)</td>
<td>124 ± 5</td>
<td>-22 ± 3‡</td>
<td>-41 ± 4‡</td>
<td>-46 ± 5‡</td>
<td>-52 ± 4‡</td>
<td>-54 ± 9‡</td>
</tr>
<tr>
<td>CO (ml/min/kg)</td>
<td>106 ± 4</td>
<td>—</td>
<td>-15 ± 4‡</td>
<td>-17 ± 5</td>
<td>-21 ± 4‡</td>
<td>-20 ± 4‡</td>
</tr>
<tr>
<td>P_{v} (torr)</td>
<td>7.0 ± 0.8</td>
<td>-1.2 ± 0.5‡</td>
<td>-3.0 ± 0.9‡</td>
<td>-3.4 ± 0.9‡</td>
<td>-3.9 ± 1.2‡</td>
<td>-2.8 ± 1.1‡</td>
</tr>
<tr>
<td>P_{cv} (torr)</td>
<td>4.8 ± 0.6</td>
<td>-0.1 ± 0.07</td>
<td>-0.3 ± 0.07</td>
<td>-0.4 ± 0.07‡</td>
<td>-0.8 ± 0.03‡</td>
<td>-0.4 ± 0.07‡</td>
</tr>
<tr>
<td>F_{v} (ml/min/100 g of liver)</td>
<td>78.5 ± 6.4</td>
<td>+8.5 ± 5.7</td>
<td>-0.6 ± 0.9</td>
<td>-16.7 ± 5.1‡</td>
<td>-19.4 ± 5.1‡</td>
<td>-16.0 ± 5.8‡</td>
</tr>
<tr>
<td>F_{cv} (ml/min/100 g of liver)</td>
<td>41.4 ± 4.1</td>
<td>+3.7 ± 2.4</td>
<td>+5.9 ± 2.4‡</td>
<td>+5.2 ± 2.2‡</td>
<td>+3.4 ± 1.5‡</td>
<td>+7.8 ± 6.7</td>
</tr>
<tr>
<td>R_{pv} (10^9 × dyn × sec × cm^-5)</td>
<td>1.2 ± 0.2</td>
<td>-0.4 ± 0.1‡</td>
<td>-0.7 ± 0.3</td>
<td>-0.8 ± 0.3‡</td>
<td>-1.0 ± 0.4‡</td>
<td>-0.9 ± 0.3‡</td>
</tr>
<tr>
<td>R_{cv} (10^9 × dyn × sec × cm^-5)</td>
<td>5.7 ± 0.8</td>
<td>-1.4 ± 0.4‡</td>
<td>-2.6 ± 0.7‡</td>
<td>-3.5 ± 0.8‡</td>
<td>-3.9 ± 1.2‡</td>
<td>-5.6 ± 2.2‡</td>
</tr>
<tr>
<td>P_{tcv}, (torr)</td>
<td>41 ± 4</td>
<td>—</td>
<td>—</td>
<td>+3 ± 2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>pH_{cv}</td>
<td>7.33 ± 0.02</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-0.02 ± 0.01</td>
<td>—</td>
</tr>
<tr>
<td>O_{2} cont. a.</td>
<td>18.14 ± 1.21</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-1.6 ± 1.8</td>
<td>—</td>
</tr>
<tr>
<td>O_{2} cont. p.v.</td>
<td>13.16 ± 1.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-1.3 ± 1.04</td>
<td>—</td>
</tr>
<tr>
<td>O_{2} cont. h.v.</td>
<td>9.80 ± 1.50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-0.7 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>O_{2} cons. h.</td>
<td>4.8 ± 0.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-0.8 ± 0.9</td>
<td>—</td>
</tr>
<tr>
<td>L/P_{a}</td>
<td>18.1 ± 3.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+2.7 ± 2.8</td>
<td>—</td>
</tr>
</tbody>
</table>

* P_{a} = mean arterial pressure; CO = cardiac output; P_{v} = portal pressure; P_{cv} = hepatic vein pressure; F_{pv} = portal blood flow; F_{cv} = hepatic blood flow; R_{pv} = portal venular resistance; R_{cv} = hepatic arteriole resistance; pH_{cv} = pH of portal blood; O_{2} cont. a. = O_{2} content, arteriole; O_{2} cont. p.v. = O_{2} content, portal vein; O_{2} cont. h.v. = O_{2} content, hepatic vein; O_{2} cons. h. = O_{2} consumption in ml O_{2}/100 ml arterial, portal and hepatic-vein blood, respectively; L/P_{a} = hepatic oxygen consumption in ml O_{2}/min/100 g of liver.

‡ p < 0.05 compared with baseline value according to t test for paired data.

Another possibility should be considered. Decreased hepatic arterial blood flow would decrease net sinusoidal blood inflow, which could decrease portal pressure. However, hepatic arterial blood flow was increased in most observations in Group I (table 1), and moreover, portal pressure decreased during SNP infusion even during conditions of steady portal blood flow and occluded hepatic artery (table 2).

The only remaining explanation for the decrease in portal pressure is that SNP decreases presinusoidal resistance. It is reasonable to propose that this comes about because of a decrease in the tone of the presinusoidal sphincter. The greater decrease in portal pressure in Group I compared with Group II can be explained by the decrease in portal blood flow in Group I and by the larger dose of SNP used.

An increase in hepatic arterial blood flow during a decrease in portal blood flow has been seen during partial or total occlusion of the portal vein, and with decreases in pH and O_{2} content of portal blood. This increase in hepatic arterial blood flow may be viewed as compensatory, functioning to limit hypoxia during circumstances of decreased portal flow.
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Fig. 1. Relationship between differences in mean arterial pressure and corresponding changes in hepatic arterial blood flow. $\Delta P_a$ = differences in mean arterial pressure in torr. $\Delta F_{ha}$ = differences in hepatic arterial blood flow in ml/min/100 g of liver. Solid dot and solid line show the relationship in Group I dogs (spontaneously changed portal blood flow).

$\Delta F_{ha} = -0.0265 - 0.3345 (\Delta P_a) - 0.0084 (\Delta P_a)^2 + 0.0002 (\Delta P_a)^2 \times 2 ; r^2 = 0.219$

$x$ and dotted line show the relationship in Group II dogs (artificially stabilized portal blood flow).

$\Delta F_{ha} = 1.620 + 0.390 (\Delta P_a) + 0.001 (\Delta P_a)^2 ; r^2 = 0.736$

The dependence of $F_{ha}$ on $P_a$ is increased ($r^2$ is increased from 0.219 to 0.736) and changed in the opposite direction during artificially stabilized portal blood flow (dotted and solid lines).

Blood flow and decreased $O_2$ content and $pH$ of portal blood.

In this study, hepatic arterial blood flow usually increased in Group I but not in Group II (table 3). The only difference between these groups was in the portal circulation. Portal blood flow was allowed to change spontaneously in Group I and was artificially stabilized in Group II. Therefore, these observations demonstrate that during SNP infusion resulting in decreases in arterial blood pressure of as much as 40 per cent the portal circulation continued to be an important factor influencing hepatic arterial circulation. The data indicate that an increase in hepatic arterial blood flow in Group I was not caused by a direct influence of SNP on the hepatic arteriolar sphincter, but by changes in portal circulation. In support of this, when portal circulation was steady, internal control mechanisms did not increase hepatic arterial blood flow because the blood and oxygen supply to the liver was adequate.

Table 2. Average Changes (± SE) in Portal Pressure ($P_p$) during Temporary Occlusion of the Hepatic Artery and Intraportal Infusion of Sodium Nitroprusside (SNP) during Conditions of Steady Portal Blood Flow (Group II)

<table>
<thead>
<tr>
<th>Period of Observation</th>
<th>Baseline Value before Occlusion (tort)</th>
<th>Changes* over Time in $P_p$ (tort)</th>
<th>Occlusion of Hepatic Artery</th>
<th>2 Min after Hepatic Artery Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before SNP Infusion</td>
<td>During SNP Infusion</td>
<td>After SNP Infusion</td>
</tr>
<tr>
<td>Changes in $P_p$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between baseline and experimental data</td>
<td>11.2 ± 1.01</td>
<td>+0.1 ± 0.17</td>
<td>−1.8 ± 0.42†‡</td>
<td>+0.1 ± 0.35‡</td>
</tr>
</tbody>
</table>

* † = increase; ‡ = decrease.
† $P < 0.05$ compared with baseline value according to t test for paired data.
‡ $P < 0.05$ compared with value in previous column according to t test for paired data.
A direct influence of SNP on hepatic arteriolar tone cannot be excluded, but it seems that its role is not remarkable. Hepatic arteriolar resistance decreased considerably in Group I, yet was not changed in Group II (table 3). The decrease in hepatic arteriolar resistance in Group I could depend solely on changes in portal circulation (portal blood flow, pH and O_2 content of portal blood). If SNP relaxed the hepatic arteriolar sphincter in Group I, the same pharmacologic effect should have occurred in Group II. It seems logical that the determining factor was portal circulation.

In Group I a decrease in arterial blood pressure was usually associated with an increase in hepatic arterial blood flow (fig. 1). However, the relationship between them was weak (r^2 = 0.219) because the portal circulation was the most important factor influencing hepatic arterial blood flow. In Group II portal circulation was eliminated as an influencing factor and the dependence of hepatic arterial blood flow on mean arterial blood pressure significantly increased (r^2 = 0.736) and even changed in the opposite direction (fig. 1).

The absence of any significant change in oxygen content in blood of the portal and hepatic veins, in oxygen consumption by the liver, and in the ratio of lactate to pyruvate produced by the liver (table 1) allows us to conclude that SNP in concentrations decreasing mean arterial blood pressure as much as 40 per cent does not lead to hepatic hypoxia. The integrity of the hepatic circulatory autoregulation mechanisms was maintained and hepatic arterial blood flow increased during SNP infusion.

A tendency of hepatic circulatory variables to return towards baseline values after 30 minutes of SNP infusion may be considered a partial escape of the hepatic vasculature from SNP influence. Total or partial escape of systemic vasculature from vasoconstricting and vasodilating influences, have been described. The nature of this response is still unclear.

We conclude that SNP in concentrations that decrease systemic blood pressure as much as 40 per cent of the baseline value does not lead to hepatic hypoxia in normal dogs. SNP decreases portal presinusoidal resistance and does not interfere with the ability of the liver to increase hepatic arterial blood flow in conditions of insufficient portal circulation.

### References

3. Michenfelder JD, Thye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane or nitroprusside. Anesthesiology 46: 188–201, 1977

APPENDIX

1) \( R_{pv} = \frac{(P_a - P_h) \times 1333}{F_{pv}} \),

where:

- \( R_{pv} \) = portal venular resistance in dynes × sec × cm⁻³
- \( P_a \) = portal and hepatic vein pressures in torr
- \( F_{pv} \) = portal blood flow in ml/min

2) \( R_{ha} = \frac{(P_a - P_h) \times 1333}{F_{ha}} \),

where:

- \( R_{ha} \) = hepatic arteriolar resistance in dynes × sec × cm⁻³
- \( P_a \) = mean arterial and hepatic vein pressure in torr
- \( F_{ha} \) = hepatic artery blood flow in ml/min.

3) \( C_{ha} = (0.0136 \times Hb \times S_{ha}) + 0.0003 \times P_{ha} \),

where:

- \( C_{ha} \) = oxygen content in ml O₂/100 ml blood
- \( Hb \) = hemoglobin in grams/100 ml of blood
- \( S_{ha} \) = oxygen saturation of hemoglobin in per cent
- \( P_{ha} \) = blood oxygen tension in torr

4) \( O_2 \) cons. h. = \( \frac{(C_{ha} \times F_{ha}) + (C_{pv} \times F_{pv}) - (C_{ha} \times F_{ha})}{100} \)

where:

- \( O_2 \) cons. h. = hepatic oxygen consumption in ml O₂/min/100 g of liver
- \( C_{ha} \) = oxygen content in blood of aorta, portal vein, and hepatic vein, respectively, in ml O₂/100 g of blood
- \( C_{pv} \) = oxygen content in portal vein
- \( C_{ha} \) = oxygen content in hepatic vein
- \( F_{ha} \) = portal and hepatic artery blood flow, respectively, in ml/min/100 g of liver

5) \( L/P_h = \frac{[L_a] \times (F_{ha} + F_{pv}) - [L_{pv}] \times F_{ha} - [L_a] \times F_{pv}}{[P_{ha}] \times (F_{ha} + F_{pv}) - [P_{pv}] \times F_{ha} - [P_{ha}] \times F_{pv}} \)

where:

- \( L/P_h \) = ratio of lactate/pyruvate produced by liver
- \( L_a \) = concentration of lactate in blood of aorta, portal vein, and hepatic vein, respectively, in mmol/l
- \( L_{pv} \) = concentration of lactate in portal vein
- \( P_a \) = concentration of pyruvate in blood of aorta
- \( P_{pv} \) = concentration of pyruvate in portal vein
- \( F_{ha} \) = portal and hepatic artery blood flow, respectively, ml/min