EFFECT OF INCREASED CONCENTRATIONS OF CARBON DIOXIDE DURING HALOTHANE ANAESTHESIA ON LIVER BLOOD FLOW AND HEPATIC OXYGEN CONSUMPTION

I. A. THOMSON, W. FITCH, R. L. HUGHES AND D. CAMPBELL

SUMMARY

The effects of hypercapnia (during halothane anaesthesia) on the hepatic circulation and hepatic oxygen consumption were investigated in anaesthetized greyhounds. The administration of 1% halothane alone caused significant decreases in both hepatic arterial and portal venous blood flows. Hepatic oxygen consumption did not change significantly. When carbon dioxide was added to the inspired gas mixture during the continued administration of halothane, hepatic arterial blood flow showed a further decrease (P< 0.01), while portal venous flow increased markedly. This resulted in an overall increase in total liver blood flow. Hepatic oxygen supply increased also. However, hepatic oxygen consumption increased during the periods of hypercapnia. Thus, although the hypercapnia increased the oxygen supply to the liver, there was no improvement in the supply: demand ratio.

A reciprocity of response has been shown, under a variety of conditions, between portal venous blood flow and hepatic arterial blood flow (Burton-Opitz, 1911; Cohn and Kountz, 1963; Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968) such that there is a concomitant increase in hepatic arterial flow (decrease in hepatic arterial resistance) as portal venous blood flow is decreased. In this way the oxygen supply to the liver is protected. However, this physiological balance is affected by the administration of volatile anaesthetics such as halothane and enflurane (Andreen, Irestedt and Zetterstrom, 1977; Hughes, Campbell and Fitch, 1980) and gaseous anaesthetic agents such as nitrous oxide (Thomson et al., 1982), since these induce simultaneous decreases in portal venous and hepatic arterial blood flows. Since decreases in the blood supply to the liver could diminish significantly the oxygen available to that organ, the present study was undertaken to assess the efficacy of hypercapnia in reversing the depressant effects of halothane on hepatic blood flow and in preserving its oxygen supply.

MATERIALS AND METHODS

Anaesthesia

Anaesthesia was induced in six greyhounds (20–30 kg) with thiopentone 20 mg kg⁻¹ i.v. and maintained with pentobarbitone 30 mg kg⁻¹ i.v. Following tracheal intubation, the lungs were ventilated artificially with a mixture of 75% nitrogen in oxygen. The minute volume of ventilation and the inspired oxygen concentration were adjusted as necessary to produce stable physiological tensions of carbon dioxide and oxygen, in arterial blood. Pancuronium bromide 0.15 mg kg⁻¹ i.v. was administered to produce neuromuscular blockade.

Surgical preparation

The surgical preparation has been described previously (Hughes et al., 1979) and the salient features are outlined below. Laparotomy was performed via a midline incision. The common hepatic artery and the portal vein were identified, cleared of adventitia and electromagnetic flowprobes (Statham) applied. Care was taken to ensure that the peri-arterial nerve plexus remained intact. The gastroduodenal and right gastric arteries were ligated to ensure that all the blood flowing through the common hepatic artery supplied the liver. A catheter, inserted to the external jugular vein, was passed into an hepatic vein. Cardiac output was measured by the thermodilution method using a triple-lumen thermistor-tipped catheter placed in the pulmonary artery. Hepatic oxygen consumption was calculated from measure-
ments of oxygen content (Lex-02-Con electrolytic cell; Lexington Instruments). Systemic vascular resistance, hepatic arterial resistance, portal venous and mesenteric vascular resistances were calculated.

Systemic arterial pressure was monitored continuously via a cannula sited in the abdominal aorta. Blood-gas tensions and acid-base balance were measured intermittently (Corning 165 blood-gas/pH analyser). Plasma halothane concentrations were measured by gas-liquid chromatography (Allott, Steward and Mapleson, 1971). Measurements were obtained under control conditions, during the administration of halothane alone and in association with each step increase in carbon dioxide tension.

**Experimental programme**

Approximately 3–4 h after the induction of anaesthesia and once the preparation had stabilized, control readings (in the absence of halothane) of hepatic arterial and portal venous blood flows, systemic arterial pressure, portal venous pressure, hepatic venous pressure and cardiac output were obtained and appropriate blood samples drawn from the abdominal aorta, portal vein and hepatic vein. The administration of 1% halothane was commenced (Fluotec Mk2) and continued for the remainder of the investigation. After 30 min, further recordings of liver blood flow and the various cardiovascular indices were obtained and blood samples drawn. A step increase in arterial carbon dioxide tension was produced by the addition of carbon dioxide to the inspired gas mixture ($P_{CO_2} = 9.3$ kPa), a series of measurements made and blood samples drawn at 1 min and at 20 min. Carbon dioxide was then discontinued and normocapnia regained. After a gap of 30 min, further measurements were obtained under halothane alone. A further step increase in carbon dioxide tension was induced ($P_{CO_2} = 12.0$ kPa) and appropriate measurements obtained. Any acidosis was corrected with sodium bicarbonate. All data obtained following halothane or halothane and hypercapnia were compared with control values using the Student’s t test for paired data. $P = 0.05$ was taken as the level of significance.

**RESULTS**

The administration of 1% halothane produced a significant decrease in mean arterial pressure (10%). Mean arterial pressure was further decreased significantly by both degrees of hypercapnia (by 23% and 28% respectively) (table I). Neither halothane, nor halothane and hypercapnia, caused any significant changes in cardiac output.

Significant decreases in hepatic arterial blood flow and portal venous blood flow were recorded when halothane was administered at normal values of $P_{CO_2}$, but these were relatively small (15% and 10% respectively). The administration of carbon dioxide (9.3 and 12.0 kPa) produced decreases in hepatic arterial blood flow which were significantly different from the control values obtained in the absence of halothane (fig. 1). Portal venous blood flow, on the other hand, increased significantly to approximately 30–50% above control, this effect being more prominent when hypercapnia had been established for 20 min (fig. 1). Thus, the overall

<table>
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<tr>
<th></th>
<th>Mean arterial pressure (mm Hg) (n=6)</th>
<th>Portal venous pressure (mm Hg) (n=6)</th>
<th>Cardiac output (litre min⁻¹ kg⁻¹) (n=5)</th>
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<tbody>
<tr>
<td>Control</td>
<td>144.5 ± 11.5</td>
<td>7.5 ± 0.5</td>
<td>0.126 ± 0.009</td>
</tr>
<tr>
<td>Halothane 1%</td>
<td>129.8 ± 12.4***</td>
<td>7.9 ± 0.8</td>
<td>0.113 ± 0.008</td>
</tr>
<tr>
<td>Halothane + hypercapnia $P_{CO_2}$ 9.3 kPa 1 min</td>
<td>112.2 ± 13.6**</td>
<td>9.6 ± 0.8*</td>
<td>0.112 ± 0.006</td>
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<td>20 min</td>
<td>110.0 ± 11.5**</td>
<td>8.9 ± 0.6*</td>
</tr>
<tr>
<td>Control</td>
<td>144.5 ± 11.5</td>
<td>7.5 ± 0.5</td>
<td>0.122 ± 0.006</td>
</tr>
<tr>
<td>Halothane 1%</td>
<td>126.5 ± 10.0*</td>
<td>7.8 ± 0.7</td>
<td>0.119 ± 0.012</td>
</tr>
<tr>
<td>Halothane + hypercapnia $P_{CO_2}$ 12.0 kPa 1 min</td>
<td>103.3 ± 12.4*</td>
<td>10.6 ± 0.9**</td>
<td>0.118 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td>104.3 ± 10.3*</td>
<td>10.3 ± 0.8**</td>
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effect on the total blood flow to the liver was that hypercapnia reversed the decrease in total liver blood flow produced by halothane alone and, indeed, the net result during hypercapnia was an increase of between 20 and 35% in total liver blood flow (fig. 1).

Systemic vascular resistance was unchanged during the administration of halothane. When hypercapnia was induced, during the continued administration of halothane, systemic vascular resistance decreased. Initially, these decreases were not significant, but after 20 min at each value of hypercapnia, systemic vascular resistance had decreased significantly by 20% and 35%, respectively (fig. 2). Hepatic arterial resistance was unchanged throughout the experiment. Mesenteric vascular resistance was unaltered by halothane alone, but was markedly decreased by hypercapnia by between 45% and 55%. These decreases were significant during both the early and the later stages of hypercapnia (fig. 2). Halothane alone caused no change in portal venous pressure, but significant increases were observed during the hypercapnic periods (table I).

Although 1% halothane alone produced no change in hepatic oxygen consumption, the total oxygen supply to the liver decreased significantly (table II). The addition of carbon dioxide (during the continued administration of the halothane) increased both oxygen consumption and oxygen supply significantly. Although the most marked increase in oxygen consumption (47%) was observed during the greater carbon dioxide tension, this was balanced by an increase in hepatic oxygen supply.

![Graph showing effects of halothane and hypercapnia on liver blood flows](image1)

**Fig. 1.** Effects of halothane and hypercapnia on liver blood flows (n = 6). C = Control; H = 1% halothane; a = 1 min at $P_{\text{CO}_2}$ 9.3 kPa and 1% halothane; b = 20 min at $P_{\text{CO}_2}$ 9.3 kPa and 1% halothane; x = 1 min at $P_{\text{CO}_2}$ 12.0 kPa and 1% halothane; y = 20 min at $P_{\text{CO}_2}$ 12.0 kPa and 1% halothane. *P < 0.05; **P < 0.01; ***P < 0.001.

![Graph showing effects of halothane and hypercapnia on vascular resistances](image2)

**Fig. 2.** Effects of halothane and hypercapnia on vascular resistances (n = 6). C = Control; H = 1% halothane; a = 1 min at $P_{\text{CO}_2}$ 9.3 kPa and 1% halothane; b = 20 min at $P_{\text{CO}_2}$ 9.3 kPa and 1% halothane; x = 1 min at $P_{\text{CO}_2}$ 12.0 kPa and 1% halothane; y = 20 min at $P_{\text{CO}_2}$ of 12.0 kPa and 1% halothane.
TABLE II. Effects (mean ± SEM) of halothane and hypercapnia on hepatic venous oxygen content and on hepatic oxygen supply, consumption and extraction. n = no. observations. *P < 0.05; **P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Hepatic ven. O₂ content (ml/dl blood)</th>
<th>Hepatic art. O₂ supply (ml min⁻¹/100 g liver)</th>
<th>Portal ven. O₂ content (ml/dl blood)</th>
<th>Total O₂ supply (ml min⁻¹/100 g liver)</th>
<th>Hepatic O₂ consumption (ml min⁻¹/100 g liver)</th>
<th>Extraction O₂ from hepatic art. blood (%)</th>
<th>Extraction O₂ from portal ven. blood (%)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>16.2 ± 1.6</td>
<td>5.7 ± 0.5*</td>
<td>22.4 ± 2.8</td>
<td>26.0 ± 3.0**</td>
<td>5.5 ± 0.7</td>
<td>23.5</td>
<td>16.1</td>
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<td>Halothane 1%</td>
<td>17.0 ± 1.2</td>
<td>6.8 ± 0.8</td>
<td>22.4 ± 2.8</td>
<td>29.2 ± 3.5</td>
<td>5.5 ± 0.8</td>
<td>27.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Halothane + hypercapnia P&lt;sub&gt;CO₂&lt;/sub&gt; 9.3 kPa</td>
<td>17.8 ± 1.1</td>
<td>4.5 ± 0.5**</td>
<td>32.3 ± 3.6***</td>
<td>36.8 ± 4.0***</td>
<td>6.9 ± 0.9*</td>
<td>23.5</td>
<td>18.2</td>
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<tr>
<td></td>
<td>18.0 ± 1.0</td>
<td>4.5 ± 0.4*</td>
<td>33.2 ± 3.8***</td>
<td>37.7 ± 4.1***</td>
<td>6.3 ± 0.7*</td>
<td>23.4</td>
<td>15.9</td>
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<tr>
<td>Control</td>
<td>17.0 ± 1.2</td>
<td>6.8 ± 0.8</td>
<td>22.4 ± 2.8</td>
<td>29.2 ± 3.5</td>
<td>5.5 ± 0.8</td>
<td>27.4</td>
<td>16.1</td>
</tr>
<tr>
<td>Halothane 1%</td>
<td>15.6 ± 1.7</td>
<td>5.3 ± 0.3</td>
<td>19.4 ± 2.8**</td>
<td>24.7 ± 3.0*</td>
<td>5.8 ± 1.2</td>
<td>33.5</td>
<td>20.9</td>
</tr>
<tr>
<td>Halothane + hypercapnia P&lt;sub&gt;CO₂&lt;/sub&gt; 12.0 kPa</td>
<td>17.6 ± 1.4</td>
<td>4.1 ± 0.5*</td>
<td>33.7 ± 4.4***</td>
<td>37.6 ± 4.4**</td>
<td>8.2 ± 1.1*</td>
<td>25.6</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>18.2 ± 1.4</td>
<td>4.3 ± 0.4*</td>
<td>37.9 ± 4.7**</td>
<td>42.2 ± 5.0**</td>
<td>7.8 ± 0.8</td>
<td>23.9</td>
<td>17.9</td>
</tr>
</tbody>
</table>

(44%). It was noted that the amount of oxygen extracted from hepatic arterial or portal venous blood was greater during the administration of halothane alone than in either the control situation or during the administration of carbon dioxide (table II). The mean plasma halothane concentration during the experiments was 10.3 mg dl⁻¹ (range 7.6–13.8 mg dl⁻¹).

**DISCUSSION**

The animal model used in these investigations has been studied previously and shown to be stable (Hughes et al., 1979). The dogs were anaesthetized principally with pentobarbitone, which has been shown to maintain a stable cardiovascular state (Gilmore, 1965) and to result in values of liver blood flow similar to those in unanaesthetized animals (Fisher et al., 1956; Gilmore, 1958; Evringham, Brenneman and Horvath, 1959). Electromagnetic flowmeters allowed accurate and reliable measurements, not only of total liver blood flow, but also of the relative contributions via the hepatic artery and portal vein. This facility provided an insight into the changes in the relationship between the two vascular supplies brought about by anaesthetic agents and by alterations in blood-gas tensions.

Pancuronium was administered in these experiments to provide adequate muscle paralysis for laparotomy. This agent may influence liver blood flow through its reported vagolytic effects (Saxena and Bonta, 1970), an inhibition of neuronal uptake of nor-adrenaline (Docherty and McGrath, 1978) and possibly through an indirect sympathomimetic action (Domenech et al., 1976). However, as a period of at least 3 h had elapsed after the administration of the pancuronium before the first measurements of liver blood flow were obtained, it seems unlikely that liver blood flow would be affected.

The effects of hypercapnia alone on liver blood flow have been recorded by various authors. Juhl and Einer-Jensen (1977) observed decreases in flow. No change or decreases in hepatic flow were noted by Epstein and colleagues (1961), while Scholtholt and Shiraishi (1970) and Dutton, Levitzky and Berkman (1976) demonstrated consistent increases in flow. Hughes and co-workers (1979) demonstrated an initial increase in liver blood flow which had returned toward control values after 20 min at the same level of hypercapnia. The results of the present investigation show that halothane depressed hepatic arterial blood flow and that during hypercapnia this was decreased further. On the other hand, hypercapnia reversed the decrease in portal venous blood flow brought about by halothane and, indeed, flow in the portal vein was increased by over 50% from control values. This large increase in portal blood flow resulted in an overall increase in total liver blood flow despite the decrease in hepatic arterial blood flow. It is conceivable that the increase...
in portal flow may have resulted from splenic contraction since this action has been attributed to carbon dioxide (Ramlo and Brown, 1959). However, these workers used much greater carbon dioxide concentrations than were used in this study and Hughes and co-workers (1979), who administered similar carbon dioxide concentrations, were unable to detect significant changes in splenic blood flow.

Hughes and colleagues (1979) suggested that the decrease in hepatic arterial flow was not a direct effect of the increases in carbon dioxide concentrations, but was a mechanical phenomenon caused by an increase in portal venous and, thus, hepatic sinusoidal pressure. An increase in sinusoidal pressure has been proposed to induce myogenic constriction of the hepatic arterioles (Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968) and increase hepatic arterial resistance. However, there was no change in hepatic arterial resistance in these experiments, despite an increase in portal venous pressure. It might seem, therefore, that the decrease in hepatic arterial blood flow was not a local phenomenon but was solely a result of the decrease in mean arterial pressure. However, a myogenic constriction of the hepatic arterioles cannot be ruled out since, despite a decrease in systemic vascular resistance of up to 35%, tone in the hepatic arterial bed was at least preserved.

The fact that halothane decreases liver blood flow is well documented (Ahlgren et al., 1967; Deutsch, 1967; Juhl and Einer-Jensen, 1974; Thulin, Andreen and Irestedt, 1975; Hughes, Campbell and Fitch, 1980) and decreases in both hepatic arterial and portal venous blood flows were observed in this study. However, the decreases in liver blood flow were quantitatively smaller than those found by Thulin, Andreen and Irestedt (1975) and Hughes, Campbell and Fitch (1980) whose work was performed under similar experimental conditions. This can be explained by the smaller plasma halothane concentrations, which were approximately 10 mg dl⁻¹ in our study compared with 20–40 mg dl⁻¹ in the other studies.

In this study, when portal venous blood flow decreased, hepatic arterial resistance was unchanged and hepatic arterial blood flow actually decreased (in association with a decrease in systemic arterial pressure). This could suggest that halothane in some way impairs the ability of the liver to compensate for any decreases in portal flow.

The unique dual blood supply to the liver provides a mechanism for maintaining blood flow under a variety of conditions. The reciprocal relationship between flow in the portal vein and hepatic artery has been observed widely. This intrinsic response of the hepatic vasculature may be overcome by the administration of exogenous compounds such as anaesthetic drugs, which can result in a decrease in flow in both vascular units. Increasing carbon dioxide tension in the greyhound overcomes this inhibition of local vasoregulatory control caused by anaesthetics such as halothane. The basic mechanisms underlying these actions remain to be explained. If anaesthetic agents affect this intrinsic response and cause a decrease in hepatic arterial blood flow, during periods when portal blood flow is also low the oxygen supply could be decreased.

Under normal conditions the oxygen supply to the liver is in excess of requirements and if the blood supply is decreased a greater proportion of the oxygen supply can be utilized. However, when hepatic function is compromised as occurs, for example, during liver disease or when blood flow is already decreased as a result of surgery itself, a further decrease in flow or in the oxygen content, or both, of arterial blood could result in the hepatic demand for oxygen outstripping supply. The potential then exists for hypoxic cell damage to occur in the hepatic parenchyma. Maintenance of adequate tissue oxygen tensions would protect liver cells from the direct toxic effects of hypoxia itself and would also prevent the reductive metabolism of halothane which has been shown to produce highly reactive metabolites which may cause hepatocellular damage (Sipes, Podolsky and Brown, 1977). The increases in liver blood flow and oxygen supply during hypercapnia, although potentially beneficial to the hepatic parenchyma, were balanced by an increase in hepatic oxygen consumption and no net gain was effected.

In conclusion, it has been shown that hypercapnia can reverse the depressant effects of halothane anaesthesia on total liver blood flow and oxygen supply. Under physiological conditions this may be of questionable significance, since hepatic oxygen consumption was increased by the hypercapnia. The relevance of this alteration in oxygen supply under pathological conditions remains to be elucidated.
ACKNOWLEDGEMENTS

We are grateful for the assistance of the nursing and technical staff of the Wellcome Surgical Institute, of Miss E. H. Polkey for typing the manuscript and of Dr R. Watson and Mr I. Macdonald for measuring plasma halothane concentrations. The study was undertaken with financial assistance from the Scottish Hospital Endowments Research Trust.

REFERENCES


EFFETS DE CONCENTRATIONS CROISSANTES DE GAZ CARBONIQUE AU COURS DE L'ANESTHESIE A L'HALOTHANE SUR LE DEBIT SANGUIN HEPATIQUE ET LA CONSOMMATION D'OXYGENE DU FOIE

RESUME

Nous avons essayé les effets de l'hypercapnie (au cours de l'anesthésie à l'halothane) sur la circulation hépatique et la consommation d'oxygène du foie. L'investigation a été conduite chez des chiens anesthésiés. L'administration de 1% d'halothane seule a provoqué une diminution significative des débits sanguins à la fois dans l'artère hépatique et dans la veine porte. La consommation hépatique d'oxygène n'était pas significativement modifiée. Lorsque l'animal recevait du dioxyde de carbone au mélange inhalé au cours de l'administration continue d'halothane, le débit de l'artère hépatique diminuait encore (P<0,01) alors que le débit dans la veine porte augmentait nettement. Ceci entraînait une augmentation globale du débit sanguin hépatique total. La quantité d'oxygène délivrée au foie augmentait ainsi. Cependant, la consommation d'oxygène par le foie augmentait pendant les périodes d'hypercapnie. Ainsi, bien que l'hypercapnie augmente la quantité d'oxygène délivrée au foie, il n'y a pas d'amélioration du rapport oxygène fourni/oxyméte consommé.
CO$_2$ AND LIVER FUNCTION WITH HALOTHANE

**WIRKUNG ANSTEIGENDER CO$_2$-KONZENTRATIONEN WÄHREND HALOTHANNARKOSEN AUF DIE LEBERDURCHBLUTUNG UND DEN SAUERSTOFFVERBRAUCH DER LEBER**

Bei narkotisierten Windhunden wurde die Wirkung von Hyperkapnie während Halothannarkosen auf die Leberdurchblutung und auf den Sauerstoffverbrauch der Leber untersucht. Die alleinige Gabe von 1% Halothan führte zu signifikantem Abstehen des Blutstroms in der Arteria hepatica und der Pfortader. Der Sauerstoffbedarf der Leber veränderte sich nicht signifikant. Bei zusätzlicher CO$_2$-Gabe fiel der Blutstrom in der Arteria hepatica noch weiter ab ($P<0.01$), während er in der Pfortader deutlich anstieg. Das führte zu einem Anstieg der totalen Leberdurchblutung und Zunahme des Sauerstoffangebots. Während der Hyperkapnie-Phasen stieg jedoch auch der Sauerstoffverbrauch in der Leber, so daß es trotz vergrößerter Sauerstoffversorgung bei Hyperkapnie keine Verbesserung des Angebot/Nachfragen-Verhältnisses gab.

**SUMARIO**

Se averiguaron los efectos de la hipercapnia (durante la anestesia por halotano) sobre la circulación hepática y el consumo hepático de oxígeno en perros galgos anestesiados. La administración de halotano al 1% solo causó descensos significantes tanto de la corriente sanguínea arterial hepática como de la corriente sanguínea venosa portal. El consumo hepático de oxígeno no se alteró de manera significativa. Cuando se añadió anhidrido carbonico a la mezcla de gas inspirada durante la administración continua de halotano, la corriente sanguínea arterial hepática demostró un descenso adicional ($P<0.01$), mientras que la corriente sanguínea venosa portal aumentaba de manera marcada. Eso resultó en un aumento global de la corriente sanguínea hepática total. La provisión de oxígeno hepático aumentó también. Sin embargo, el consumo de oxígeno hepático aumentó durante los periodos de hipercapnia. Entonces, aunque la hipercapnia aumentó la provisión de oxígeno al higado, no hubo mejora en la relación oferta/demanda.