Effects of Hypocapnia and Hypercapnia on Splanchnic Circulation and Hepatic Function in the Beagle

Yoshihisa Fujita, MD, Takayuki Sakai, MD, Akiyuki Ohsumi, MD, and Masuhiko Takaori, MD

FUJITA Y, SAKAI T, OHSUMI A, TAKAORI M. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. Anesth Analg 1989;69:152–7.

The effects of mild hypocapnia ($Paco_2$ 22 mm Hg) and hypercapnia ($Paco_2$ 59 mm Hg) on the splanchnic circulation and hepatic function were studied in six pentobarbital anesthetized, laparotomized, mechanically ventilated beagles. Tidal volume and respiratory frequency were held constant throughout the measurements. Hepatic artery blood flow (HABF) and portal vein blood flow (PVBF) were measured by electromagnetic flowmeters. Hepatic function was assessed by indocyanine green (ICG) elimination kinetic analysis after intravenous injection of the dye. Hypocapnia caused a decrease in HABF without affecting the systemic circulation. Hypercapnia, on the other hand, caused a significant increase in cardiac output without changing mean arterial pressure. There was a significant increase in PVBF and total hepatic blood flow (THBF = PVBF + HABF). Despite the increases in PVBF and THBF, the half-life of ICG was significantly longer during hypercapnia (9.09 ± 0.79 min) than during hypocapnia (7.16 ± 0.37 min), and plasma ICG clearance was smaller during hypercapnia (4.79 ± 0.44 $ml \cdot min^{-1}$) than during hypocapnia (5.44 ± 0.33 $ml \cdot min^{-1}$) or normocapnia (5.27 ± 0.50 $ml \cdot min^{-1}$), indicating the depressed hepatic function during hypercapnia. We conclude that mild hypocapnia decreases HABF without affecting hepatic function and that mild hypercapnia is associated with a depression of hepatic function in spite of the increases in PVBF and THBF.

Key Words: CARBON DIOXIDE—hypercarbia, hypocarbia. LIVER—blood flow, function.

The effects of carbon dioxide tension on the cardiovascular system have been studied extensively in dogs and humans (1–4). Hypocapnia causes vasoconstriction directly with either slight or no depression of myocardial contraction (4). Hypercapnia, on the other hand, causes a decrease in vascular resistance by direct vasodilation and an increase in myocardial contraction through stimulation of sympathetic nerve activity, resulting in a significant increase in cardiac output (1,2).

In contrast to the overall cardiovascular system, regional hemodynamic responses to alterations in $Paco_2$ are less completely understood. The regional hemodynamic response may differ from organ to organ because of the differences in vascular responsivity to $Paco_2$. Sympathetic innervation of the organs may also modify the regional hemodynamic response. In addition, $Paco_2$-induced alterations in overall cardiovascular hemodynamics also influence the regional hemodynamic response.

This study focuses on the hemodynamic responses of the splanchnic circulation to alterations in $Paco_2$, because this circulation receives the largest portion of cardiac output and plays a central role in maintaining the stability of the systemic circulation. The modification of sympathetic nerve activity caused by alterations in $Paco_2$ appears to affect the splanchnic circulation substantially, since the splanchnic vasculature is richly innervated by sympathetic nerve fibers originating from the splanchnic nerves and its importance in the regulation of the splanchnic circulation is already well recognized (5–7).

Effects of $Paco_2$ on hepatic function are also important for the preservation of hepatic function in patients during mechanical ventilation. Patients are commonly ventilated at a hypocapnic level during

Supported in part by Kawasaki Medical School Project Grant #62-1006 and by Grant #63480354 from the Ministry of Education for Scientific Research.

Received from the Department of Anesthesiology, Kawasaki Medical School, Okayama, Japan. Accepted for publication February 10, 1989.

Address correspondence to Dr. Fujita, Department of Anesthesiology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-01 Japan.

general anesthesia or intensive therapy, whereas hypercapnia is often seen despite mechanical ventilation, especially in patients with chronic obstructive lung diseases. To the best of our knowledge, however, hepatic function during mechanical ventilation at hypocapnic or hypercapnic levels has not been assessed in conjunction with changes in the splanchnic circulation.

The present study was undertaken to elucidate the effects of alterations in $Paco_2$ on both the splanchnic circulation and hepatic function under mechanical ventilation.

Materials and Methods

The experimental protocol was approved by the institutional Animal Research committee. The study was performed in six beagle dogs of both sexes (9.4 ± 0.6 kg, mean ± SEM). Anesthesia was induced with pentobarbital 30 $mg \cdot kg^{-1}$ iv and the trachea intubated with a cuffed endotracheal tube. The animals were ventilated using a constant volume respirator (R-60, Aika, Japan) with a mixture of oxygen and nitrous oxide (1:2). Muscle paralysis was maintained with pancuronium bromide, 2 mg iv initially with half of the initial dose given again as required. Pentobarbital (60 mg) was supplemented at the end of surgical preparations, which lasted about 2 hr. Metabolic acidosis was corrected only at the end of surgical preparations by sodium bicarbonate iv using doses calculated from the base excess. Body temperature was maintained between 36.0–38.0°C with a warming blanket throughout the experiment.

Surgical Preparations

A catheter was inserted into the aorta via the femoral artery for monitoring of mean arterial pressures (MAP) and for blood sampling. A 5 Fr. flow directed three lumen thermodilution catheter (Model SP5105, Gould, USA) was inserted via the right femoral vein into the pulmonary artery. The proximal port of the catheter was placed in the thoracic inferior vena cava as confirmed by injecting contrast material under fluoroscopic monitoring. This catheter was used for determination of cardiac output (CO) by the thermodilution technique and for measurement of inferior vena cava pressure (CVP). Another catheter was advanced into the hepatic vein via the right external jugular vein, the position of which was confirmed in the same way. This catheter was used for sampling of hepatic venous blood.

A laparotomy was performed along the 12th right costal margin, and a catheter was advanced into the portal vein through a branch of the splenic veins for portal vein pressure (Ppv) measurement and blood sampling. The common hepatic artery was exposed by blunt dissection. During the dissection, we tried to keep the periarterial nerves as intact as possible, thereby preserving sympathetic control of liver blood flow. After ligation of the gastroduodenal artery and vein, cuff-type electromagnetic flow probes (6 mm and 3 mm in diameter) were applied around the portal vein and the common hepatic artery respectively, and their blood flows, portal vein blood flow (PVBF), and hepatic artery blood flow (HABF), were measured with a dual electromagnetic flow meter (MF-27, Nihon-Kohden, Japan). The accuracy of blood flow measurement using these electromagnetic flow probes had been checked previously in vitro and their calibration factors were adjusted. The zero reference was obtained by temporal clamp of the vessels in vivo at the beginning of the experiment. Total hepatic blood flow (THBF) was derived from the sum of PVBF and HABF.

Assessment of Hepatic Function

Hepatic function was assessed by indocyanine green (ICG) elimination kinetic analysis as described by Matuschak et al. (8). ICG in a dose of 0.25 $mg \cdot kg^{-1}$ was rapidly injected into the inferior vena cava through the proximal portion of the three lumen pulmonary artery catheter. Arterial blood samples were withdrawn 2, 4, 6, and 8 min after injection. The plasma concentrations of ICG were determined at 805 nm using a spectrophotometer (100-60 Type, Hitachi, Japan). The hepatic function variables including the half-life of ICG($ICG_{t1/2}$), distribution volume (Vd), and fractional clearance of ICG($C_{P,ICG}$), were calculated using a one-compartment open model (8,9).

Experimental Protocol

The respiratory rate was fixed at 20 breaths per minute. Tidal volume was adjusted to obtain normocapnia ($Paco_2$ = 38–42 mm Hg) by adding a 97 mL dead space to the endotracheal tube. Hypocapnia was induced by ventilation without the dead space and hypercapnic ventilation was induced by adding carbon dioxide to the inspired gas to maintain the $Paco_2$ around 60 mm Hg without changing the tidal volume. The adjustment of carbon dioxide flow was aided by measurement of end-tidal Pco_2 using an

infrared carbon dioxide analyzer (Medical gas analyzer LB-2, Beckman, USA). Normocapnic ventilation was carried out for 60 min before starting the study. The study was performed at three different levels of $Paco_2$: hypocapnia, normocapnia, and hypercapnia. The order of the three ventilatory conditions was randomized using a Latin square sequence. Each ventilatory condition was maintained for 50 min. Hemodynamic measurements and blood samplings were performed at 30 min and ICG was injected at 40 min, followed by serial arterial samplings for determination of the ICG concentrations. Arterial and venous pressures were measured during the end-expiratory phase.

Calculations

Oxygen contents in peripheral arterial, portal, and hepatic venous blood were calculated using the following formula: Oxygen content ($ml \cdot 100\ mL^{-1}$ blood): $C = 1.34 \times Hb \times \%Sat + 0.003 \times Po_2$.

Hemoglobin saturation was calculated from Po_2 corrected for pH and temperature by the Po_2-oxygen % saturation nomogram. Oxygen delivery to the liver ($O_2h.del$), oxygen uptake by the liver ($O_2h.up$), and the oxygen deliver/uptake ratio (O_2del/up) were calculated from PVBF, HABF, and oxygen contents in portal vein, hepatic artery, and hepatic vein blood using the formula of Gelman et al. (10) without correction for liver weight.

Statistics

All data are presented as the means ± standard errors of the means. Statistical comparisons of data on hemodynamics, hepatic function, and blood gas tensions during normocapnia, hypocapnia, and hypercapnia were performed using two-way analysis of variance (ANOVA). Pairwise comparisons between means were done by the Fisher's least significant difference (LSD) method. Statistical significance was defined as $P < 0.05$.

Results

Blood Gas Tensions, pH, and O_2 Delivery and Uptake

Blood gas and pH data during the three stages of ventilation are summarized in Table 1. The $Paco_2$ levels were 39.1 ± 1.8, 22.1 ± 1.5, and 59.6 ± 3.2 mm Hg during normocapnia, hypocapnia, and hypercapnia respectively. Alterations in arterial Pco_2 were accompanied by corresponding pH changes (7.51 ± 0.02, 7.37 ± 0.01, 7.22 ± 0.02). Arterial Po_2 was, on the other hand, similar during the three stages of ventilation. Portal and hepatic venous blood pH, Pco_2, and Po_2 data during hypo- and hypercapnia differed significantly from those obtained during normocapnia. $O_2h.del$ was in the order of hypocapnia < normocapnia < hypercapnia. $O_2h.up$ during hypercapnia was significantly lower than during hypocapnia and O_2del/up was significantly greater than during hypocapnia.

Table 1. Blood Gas Tensions, pH and Oxygen Delivery and Uptake during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
Arterial blood			
pH	7.51 ± 0.02*	7.37 ± 0.01	7.22 ± 0.02*†
Pco_2 (mm Hg)	22.1 ± 1.5*	39.1 ± 1.8	59.6 ± 3.2*†
Po_2 (mm Hg)	141 ± 10	146 ± 6.0	141 ± 7.9
Portal venous blood			
pH	7.47 ± 0.02*	7.32 ± 0.02	7.19 ± 0.02*†
Pco_2 (mm Hg)	28.3 ± 1.9*	46.4 ± 3.4	65.7 ± 3.2*†
Po_2 (mm Hg)	47.2 ± 3.3*	54.7 ± 3.5	66.8 ± 6.2*†
Hepatic venous blood			
pH	7.44 ± 0.03*	7.31 ± 0.02	7.17 ± 0.02*†
Pco_2 (mm Hg)	32.5 ± 2.6*	51.3 ± 2.8	73.2 ± 4.1*†
Po_2 (mm Hg)	32.8 ± 3.6*	44.2 ± 3.8	50.7 ± 2.6*†
$O_2h.del$ ($mL \cdot min^{-1}$)	40.7 ± 4.7*	52.5 ± 6.7	55.0 ± 5.5†
$O_2h.up$ ($mL \cdot min^{-1}$)	12.3 ± 1.7	11.0 ± 1.0	9.5 ± 1.9†
O_2del/up	3.6 ± 0.6	4.8 ± 0.5	7.3 ± 1.6†

Values are mean ± SEM.
*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$; $O_2h.del$ = O_2 delivery to the liver; $O_2h.up$ = O_2 uptake by the liver; O_2del/up = O_2 delivery to uptake ratio.

Effects on Systemic and Splanchnic Hemodynamics (Table 2)

During hypocapnia there were no significant changes in systemic hemodynamics. In splanchnic hemodynamics, however, HABF was significantly lower during hypocapnia (80 ± 14 $ml \cdot min^{-1}$) than during normocapnia (120 ± 26 $ml \cdot min^{-1}$). Hypercapnia, on the other hand, was accompanied by substantial changes in both splanchnic and systemic hemodynamics. Hypercapnia caused a significant increase in CO from 1.05 ± 0.08 to 1.23 ± 0.07 $l \cdot min^{-1}$ (normocapnia and hypercapnia, respectively), while MAP was unchanged. PVBF during hypercapnia (240 ± 25 $ml \cdot min^{-1}$) was significantly greater than it was during normocapnia (182 ± 13 $ml \cdot min^{-1}$), whereas there

Table 2. Hemodynamic Variables during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
MAP (mm Hg)	143 ± 3	142 ± 5	143 ± 4
CVP (mm Hg)	4.2 ± 0.5	4.2 ± 0.3	4.2 ± 0.4
CO ($l \cdot min^{-1}$)	1.09 ± 0.15	1.05 ± 0.08	1.23 ± 0.07*†
Ppv (mm Hg)	9.5 ± 0.4	10.4 ± 0.9	12.5 ± 0.8*†
HABF ($mL \cdot min^{-1}$)	80 ± 14*	120 ± 26	97 ± 23
PVBF ($mL \cdot min^{-1}$)	177 ± 17	182 ± 13	240 ± 25*†
THBF ($mL \cdot min^{-1}$)	252 ± 20	302 ± 31	337 ± 21*†

Values are mean ± SEM.
*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$.
MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; HABF = hepatic artery blood flow; PVBF = portal vein blood flow; THBF = total hepatic blood flow; Ppv = portal vein pressure.

Table 3. Hepatic Function during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
$C_{P,ICG}$ ($mL \cdot min^{-1}$)	5.44 ± 0.33	5.27 ± 0.50	4.79 ± 0.44*†
$ICG_{t1/2}$ (min)	7.16 ± 0.37	7.78 ± 0.69	9.09 ± 0.79†
Vd ($mL \cdot kg^{-1}$)	55.4 ± 1.9	57.0 ± 2.8	60.6 ± 2.3

Values are mean ± SEM.
*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$.
$C_{P,ICG}$ = plasma ICG clearance; $ICG_{t1/2}$ = half-life of indocyanine green; Vd = distribution volume.

was no difference in HABF. THBF was significantly greater during hypercapnia (337 ± 21 $ml \cdot min^{-1}$) than during normocapnia (302 ± 31 $ml \cdot min^{-1}$). Ppv during hypercapnia was also significantly greater than it was during normocapnia (12.5 ± 0.8, 10.4 ± 0.9 mm Hg).

Hepatic Function

The results of ICG elimination kinetic analysis are summarized in Table 3. Vd, which reflects the total plasma volume, was similar during the three levels of ventilation. There were no differences in the hepatic function variables during hypocapnia and normocapnia. $ICG_{t1/2}$ was significantly longer (9.09 ± 0.79 min) during hypercapnia than during hypocapnia (7.16 ± 0.37 min) and $C_{P,ICG}$ during hypercapnia was significantly less (4.79 ± 0.44 $ml \cdot min^{-1}$) than during hypocapnia (5.44 ± 0.33 $ml \cdot min^{-1}$) and normocapnia (5.27 ± 0.50 $ml \cdot min^{-1}$).

Discussion

Because changes in airway pressure may substantially affect splanchnic hemodynamics by changing hepatic venous pressure or compression of the liver (11,12), it was essential to maintain constant airway pressure during our study of the effects of hypo- and hypercapnia on splanchnic hemodynamics and hepatic function during mechanical ventilation. We determined the tidal volume necessary to maintain normocapnia while respiratory frequency was kept constant (20 bpm) by connecting a dead space to the endotracheal tube. Hypocapnia was achieved using the same ventilatory frequency but without the dead space, and hypercapnia occurred when CO_2 was added to the inspired gas. As a result, the tidal volume and respiratory frequency remained unchanged throughout the experiment and thus changes in airway pressure during hypocapnic, normocapnic, and hypercapnic ventilations were minimized.

Though the hemodynamic responses of the splanchnic circulation to alteration of $Paco_2$ occurs maximally in a few minutes, it stabilizes within 20 min (13). The animals in our study were, therefore, considered to be in a steady state when hemodynamic and ICG measurements were carried out.

In this study, we used pentobarbital and nitrous oxide for anesthesia, and pancuronium for muscle relaxation. The effects of these drugs, therefore, should be considered when interpreting our results. To the best of our knowledge, however, pancuronium and nitrous oxide do not significantly affect the splanchnic circulation, if at all (14). Pentobarbital IV is, on the other hand, known to cause substantial depression of the cardiovascular system. We cannot thus exclude the possibility that pentobarbital may have modified the response of the splanchnic circulation to hyper- and hypocapnia. However, we presume that it did not affect the results in this study, since pentobarbital was used only for the induction of anesthesia, i.e., about 3 hr before the measurements were begun, and because the Latin square design chosen for our study may have contributed to reduction of errors related to different anesthetic depths.

There were three major findings in this study. First, the hemodynamics in both the splanchnic and systemic circulations were not significantly affected during hypocapnia except for a decrease in HABF. Second, hypercapnia caused significant changes in both the systemic and splanchnic circulations (increases in CO, PVBF, THBF, and Ppv). Third, $C_{P,ICG}$ was less during hypercapnia than it was during normo- or hypocapnic ventilation, while $ICG_{t1/2}$ was significantly greater during hypercapnia than during hypocapnia, thus indicating a decrease in hepatic ICG uptake during hypercapnia.

It is well established that hypocapnia is associated

with relatively small changes in systemic hemodynamics in anesthetized humans and animals (1,2,15). Our findings in the systemic circulation during hypocapnia are consistent with previous observations. In the splanchnic circulation, HABF decreased significantly in the present study during hypocapnia, while PVBF was unaltered.

The data in this study differ from those of Johnson (11), who reported decreases in both PVBF and HABF using electromagnetic flowmeters during hypocapnic hyperventilation in dogs. This discrepancy may be explained by the difference in the experimental conditions, since the tidal volume and respiratory frequency were changed in his experiment, while they were held constant in our study. Our results also contradict the data of Gelman et al. (16), who reported that hypocapnia increases HABF in the monkey, while cardiac output and arterial blood pressure remained unchanged, as in our study. The increase in HABF in their study was attributed to the autoregulatory response of the liver compensating for the decrease in PVBF to maintain O_2 delivery to the liver. While they used the microsphere technique for hepatic blood flow measurement without laparotomy, we measured HABF directly with an electromagnetic flow meter. It may, therefore, be possible that the surgical interventions, including laparotomy and application of electromagnetic flow probes in our study may have resulted in the different response of HABF to hypocapnia (17,18), and that the difference may be attributed to the difference in the nutritive flow (the microsphere technique) and total flow (electromagnetic flow meter).

In contrast to hypocapnia, hypercapnia caused significant changes in the systemic circulation as well as in the splanchnic circulation. Hypercapnia increased CO without affecting MAP. These results are similar to those of previous reports (2,19) and suggest the vasodilatory effect of hypercapnia and increased myocardial contraction is secondary to increased activity of the sympathetic nervous system (2).

The marked increase in PVBF during hypercapnia was considered to reflect vasodilation in the mesenteric vascular system because MAP and CVP remained unchanged. Because the mesenteric vasculature is abundantly innervated by sympathetic vasoconstrictor fibers originating from the splanchnic nerves, an increase in activity of the sympathetic nervous system should cause mesenteric vasoconstriction. The data in this study indicate, however, that the sympathetic vasoconstrictor effect does not play a major role in the splanchnic hemodynamic response during hypercapnia, and this is perhaps due to a greater direct vasodilatory effect of hypercapnia on the mesenteric vasculature.

The decrease in HABF during hypercapnia may be explained by the autoregulatory mechanism whereby the hepatic artery and portal vein adjust their flows reciprocally to maintain a constant total inflow to the liver (20). Thus, HABF may have decreased in response to the increase in PVBF during hypercapnia.

Hepatic uptake of exogenous substances is one of the most important functions of the liver. Hepatic function has been evaluated by ICG elimination kinetics by several authors (8,9), because ICG is extracted solely by hepatocytes and ICG in the doses usually used can be repeatedly administered without cellular saturation (21). ICG elimination is dependent on the liver blood flow and the ability of hepatocytes to extract the dye (22). Our data showed that $ICG_{t1/2}$ was significantly longer during hypercapnia than that during hypocapnia, and that $C_{P,ICG}$ was less during hypercapnia than normocapnia or hypocapnia. As THBF was significantly greater during hypercapnia than during hypocapnia or normocapnia, the increased $ICG_{t1/2}$ during hypercapnia appears to be an indication of the reduced ability of hepatocytes to extract the dye from blood, i.e., reduced hepatic function. Using a sulfobromophthalein, Epstein et al. (23) also observed a reduction of clearance and extraction by the liver during hypercapnia in humans, although estimated hepatic blood flow did not change significantly in their study. O_2h.up during hypercapnia in our study was also significantly less than it was during hypocapnia, though O_2h.del increased significantly during hypercapnia. The decrease in O_2h.up during hypercapnia coincides with depression of hepatic function. A similar discrepancy between THBF and ICG elimination have been reported during halothane anesthesia by Gelman et al. (9). From the ICG elimination kinetic data, they inferred that halothane affects hepatic function adversely.

Most of ICG in plasma is bound to α1-lipoproteins (24). ICG is thought to be extracted from blood into hepatocytes by carrier-mediated transport, as are other organic anions such as bilirubin and BSP, because the hepatic uptake of the anions is saturable with increasing dose, relatively selective and mutually competitive, and because countertransport of the organic anions from hepatocytes to plasma occurs (25).

There are several possible explanations for the prolongation of $ICG_{t1/2}$ and the decrease in $C_{P,ICG}$ during hypercapnia. First, acidosis during hypercapnia may be responsible for the decreased uptake of the dye. If acidosis affects the affinity of ICG for α1-lipoproteins and dissociation of the ICG becomes more difficult, a decreased ICG uptake by the hepa-

tocytes may result without compromising hepatic function. Stollman et al. (26), however, showed that albumin binding does not affect hepatic uptake of bilirubin. For this reason, changes in the affinity of ICG for α1-lipoproteins during hypercapnia is probably not an important factor for the decreased uptake of the dye. A second explanation may be that the increased activity of the sympathetic nerve induced by hypercapnia may suppress the hepatic uptake of the dye. Recently, a close correlation between sympathetic nerve activity and hepatic function was found from the evidence that sympathetic nerve stimulation induces the hepatic glycogenolysis, which is mediated via α-receptors on the hepatocytes membrane (27). Finally, liver microcirculation may be altered by hypercapnia. Hypercapnia may dilate capillaries in the liver and thereby increase the intrahepatic shunts, which would lead to a depression of the hepatic function and an increase in THBF. If correct, this hypothesis would explain the increase in THBF, the depression of the hepatic function, and the decrease in O_2h.up.

In contrast to hypercapnia, there was no significant difference in ICG elimination kinetics during hypocapnia and normocapnia despite a decrease in HABF. This suggests that the hepatic function is preserved during mild hypercapnia.

In conclusion, we demonstrated that mild hypercapnia is accompanied by significant increases in CO, PVBF, and THBF with significant vasodilation in the systemic and mesenteric vasculature, and that mild hypocapnia has no significant effects on the systemic and splanchnic circulations except for a decrease in HABF. ICG elimination kinetic data suggest a reduction in the hepatic function to extract the dye despite the increase in THBF during hypercapnia.

We are indebted to Kaori Nakayama, PharmD for technical assistance, to Naoko Moriya for preparation of the manuscript, and to Associate Professor Seizaburo Arita of the Department of Mathematics of Kawasaki Medical School for advice and help in statistical analysis.

References

1. Price HL. Effects of carbon dioxide on the cardiovascular system. Anesthesiology 1960;6:652–63.
2. Cullen DJ, Eger E II. Cardiovascular effects of carbon dioxide in man. Anesthesiology 1974;41:345–9.
3. Prys-Roberts C, Kelman GR, Greenbaum R, Kain ML, Bay J. Hemodynamics and alveolar-arterial PO_2 difference at varying $PaCO_2$ in anesthetized man. J Appl Physiol 1968;25:80–7.
4. Theye RA, Milde JH, Michenfelder JD. Effect of hypocapnia on cardiac output during anesthesia. Anesthesiology 1966;27: 778–82.
5. Carneiro JJ, Donald DE. Changes in liver blood flow and blood content in dogs during direct and reflex alteration of hepatic sympathetic nerve activity. Circ Res 1977;40:150–7.
6. Greenway CV, Stark RD. Hepatic vascular bed. Physiol Rev 1971;51:23–65.
7. Fujita Y. Splanchnic circulation following coeliac plexus block. Acta Anaesthesil Scand 1988;32:323–7.
8. Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 1987;62:1377–83.
9. Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane anesthesia and halothane anesthesia. Anesthesiology 1984;61:726–30.
10. Gelman S, Ernst E. Hepatic circulation during sodium nitroprusside infusion in the dog. Anesthesiology 1978;49:182–7.
11. Johnson EE. Splanchnic hemodynamic response to passive hyperventilation. J Appl Physiol 1975;38:156–62.
12. Hughes RL, Mathie RT, Fitch W, Cambell D. Liver blood flow and oxygen consumption during hypocapnia and IPPV in the greyhound. J Appl Physiol 1979;47:290–5.
13. Mathie RT, Blumgart LH. Effect of denervation on the hepatic haemodynamic response to hypercapnia and hypoxia in the dog. Pflügers Arch 1983;397:152–7.
14. Batchelder BM, Cooperman LH. Effects of anesthetics on splanchnic circulation and metabolism. Surg Clin North Am 1975;55:787–94.
15. Foëx P, Prys-Roberts C. Effect of CO_2 on myocardial contractility and aortic input impedance during anaesthesia. Br J Anaesth 1975;47:669–78.
16. Gelman S, Fowler KC, Bishop SP, Smith LR. Cardiac output distribution and regional blood flow during hypocarbia in monkeys. J Appl Physiol 1985;58:1225–30.
17. Gelman S. General anaesthesia and hepatic circulation. Can J Physiol Pharmacol 1986;65:1762–79.
18. Gelman S, Dillard ED, Bradley EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. Anesth Analg 1987;66:936–43.
19. Hughes RL, Mathie RT, Campbell D, Fitch W. Effect of hypercarbia on hepatic blood flow and oxygen consumption in the greyhound. Br J Anaesth 1979;51:289–96.
20. Richardson PD, Withrington PG. Liver blood flow I. Intrinsic mechanism and nervous control for liver blood flow. Gastroenterology 1981;81:159–73.
21. Paumgartner G. The handling of indocyanine green by the liver. Schweiz Med Wochenschr 1975;17(suppl.):105–27.
22. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 1975;18:378–90.
23. Epstein RM, Wheeler HO, Frumin MJ, Habif DV, Papper EM, Bradely SE. The effect of hypercapnea on estimated hepatic blood flow, circulating splanchnic blood volume, and hepatic sulfobromophthalein clearance during general anesthesia in man. J Clin Invest 1961;40:592–8.
24. Baker KJ. Binding of sufobromophthalein (BSP) sodium and indocyanine green (ICG) by plasma α1 lipoprotein. Proc Soc Exp Biol Med 1966;122:957–63.
25. Schrschmidt BF, Waggoner JG, Berk PDA. Hepatic organic anion uptake in the rat. J Clin Invest 1975;56:1280–92.
26. Stollman YR, Gaertner U, Theilmann L, Ohmi N, Wolkoff AW. Hepatic bilirubin uptake in the isolated perfused rat liver is not facilitated by albumin binding. J Clin Invest 1983;72:718–23.
27. Carceau D, Yamaguchi N, Goyer R, Guitard F. Correlation between endogenous noradrenaline and glucose released from the liver upon hepatic stimulation in anaesthetized dogs. Can J Physiol Pharmacol 1984;62:1086–91.