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Central and regional blood flow during hyperventilation

An experimental study in the pig

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Mechanical hyperventilation not only reduces brain oedema after neurotrauma but also affects the central and systemic circulation. We have, in pigs, measured blood flow in the pulmonary artery, the portal vein and in the femoral artery, as well as estimated the splanchnic blood flow and studied the relative perfusion using the microsphere technique in normo- and hypocarbia during intermittent positive pressure ventilation. A normoventilated control group did not change in cardiac output, portal vein blood flow, splanchnic blood flow and femoral arterial blood flow. Hyperventilation was performed to a P_{CO_2} of 3.0 ± 0.1 kPa. We found that in pigs ventilated with high tidal volume skeletal muscle blood flow did not change during the first 60 min of hyperventilation but gradually decreased thereafter. Blood flow to the cerebellum decreased soon after the induction of hyperventilation, whereas the cerebral blood flow did not decrease until the second hour of hyperventilation. Cardiac output, splanchnic perfusion and portal vein blood flow all decreased. Myocardial perfusion and arterial blood flow to spleen and kidney decreased while pancreatic and liver arterial blood flows were unaffected. It is concluded that mechanical hyperventilation with low frequency and large tidal volumes reduces the flow to most tissues, where the relative decrease according to microsphere measurements is most pronounced in skeletal muscles, heart muscle and cerebellum. However, the changes in cardiac output and splanchnic blood flow were not observed when hyperventilation was induced by increased frequency, keeping the tidal volume constant.

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Mechanical hyperventilation is an established method for reducing intracranial pressure and cerebral blood flow in neurosurgical patients with brain oedema (1, 2). In anaesthesia and intensive care, patients are often ventilated at a moderate degree of hypocapnia. The respiratory alkalosis or hypocapnia causes vasoconstriction of cerebral vessels but also increases tone in other arteries such as the coronary vessels (3–6). Respiratory alkalosis affects the central circulation causing a reduction in pressure and flow at least in situations with high pulmonary pressure (7). It has been advocated that low P_{aCO_2} increases muscular blood flow (8) while others state that hypocarbia decreases flow in the gastrointestinal tract, to the myocardium and the central nervous system (9). Distribution to other organs has been studied in dogs and humans (8, 10, 11). The effects of hypocapnia and hyperventilation on blood pressure, resistance and oxygen consumption in the splanchnic area of dogs (12) suggest that it is primarily the mesenteric oxygen consumption and vascular resistance and not the liver that are affected by passive hyperventilation.

The present study was undertaken to investigate the distribution of cardiac output during induced mechanical hyperventilation and the ensuing hypocarbia in an experimental setting closely related to what is practised in the clinical milieu.

MATERIAL AND METHODS

Animals, anaesthesia and surgical procedures

The study was approved by the Institutional Review Board for animal experimentation at the Uppsala University, and the care and handling of the animals were in accordance with National Institute of Health guidelines for the use of experimental animals. Thirty-one piglets of Swedish native breed, 8–14 weeks of age, weighing 18–36 kg and of both sexes were investigated. The piglets were premedicated with pentobarbital 10 $mg \cdot kg^{-1}$ body weight intraperitoneally. Anaesthesia was induced with 500 mg ketamine hydrochloride given intravenously (i.v.), and 0.5 mg of atropine to avoid salivation. Anaesthesia was maintained by continuous i.v. infusion of pentobarbital (Mebumal® VET, ACO) at the dose rate 2–4 $mg \cdot kg^{-1} \cdot h^{-1}$ and

pancuronium bromide (Pavulon®, Organon) 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$. Intravascular polyethylene catheters were inserted into the internal jugular vein, with its tip in the right atrium, into the carotid artery with the tips in the aortic arch and the left ventricle, and into the femoral artery. The pulmonary artery was catheterised with a triple-lumen Swan-Ganz catheter (CV 600-45, 7 Fr. Cardiovascular Instruments Ltd, London, England). In 21 of the pigs a catheter to the hepatic vein was placed under fluoroscopic control. In 12 animals hind limb blood flow was determined as femoral artery blood flow measured electromagnetically (Flowmeter Narcomatic RT 500, 4 mm probe).

The body temperature was monitored in the pulmonary artery and in the portal vein by thermistors and was kept within normal limits by external heating. Tracheotomy was performed and the animals were ventilated by a Servo 900C ventilator (Siemens-Elema®, Solna, Sweden). Ventilation was adjusted after analysis of arterial blood gases and the end-tidal CO_2 was monitored (Siemens CO_2 analyser, model 130, Solna, Sweden). The portal blood flow of 15 pigs was studied using the thermodilution technique.

Hepatic blood flow was measured by means of a constant infusion of indocyanine (Cardio-Green®) into the pulmonary artery at a rate of 0.3 $mg \cdot min^{-1}$ (13, 14). After a minimum of 15 min of constant infusion of dye, paired samples were drawn in triplicate from the hepatic vein and the carotid artery. After centrifugation the concentration of indocyanine green was determined spectrophotometrically. Haematocrit was determined from arterial blood samples at each measurement (15). Splanchic blood flow (ESBF) was then calculated from the concentration of dye in the infused solution *(Ci)* hepatic venous plasma *(C_h)* and arterial plasma *(Ca)*.

$$ESBF = \frac{Fi(Ci\text{-}Ch)}{(Ca\text{-}Ch)\ (1\text{-}EVF)}$$

(Ca-Ch) was the mean of three pairs of samples.

In fifteen animals laparotomy was performed through a midline incision. A 5 Fr. thermodilution catheter was then placed through an introducer into the ileocolic vein, secured by sutures in the vessel wall, and with the tip of the catheter placed in the portal vein 3 cm from the liver hilus (16, 17). To cover the fluid losses during the study, physiological saline 10 $ml \cdot kg^{-1}$ b.w. $\cdot h^{-1}$ was given to all the animals. The piglets that underwent laparotomy also received dextran (Macrodex®, KABI Pharmacia AB) 5 $mg \cdot kg^{-1} \cdot h^{-1}$, to cover the extra fluid loss during preparation.

Measurements

Arterial, right atrial, pulmonary arterial and, in ten piglets, left atrial pressures were measured by means of transducers (EMT33, Elema-Sjönander, Stockholm, Sweden and P50 Gould) during ventilation. The signals were recorded on a multi-channel jet ink recorder (Mingograph 81, Elema-Sjönander, Stockholm, Sweden), the mean pressures being obtained by electronic dampening of the signals. With a Swan-Ganz thermistor catheter connected to computers (COC-34, Cardiovascular Instruments Ltd, London, England) cardiac output, and in 15 pigs portal venous flow, were determined using the thermodilution technique. The thermal indicator used was 5 ml of normal saline chilled to 0°C, injected with an automatic syringe (ATI 1, U-lab, Stockholm, Sweden). The injection time was 2.5 s. The mean values of three measurements or more are presented. Arterial blood samples were analysed for arterial oxygen tension (Pao_2), arterial carbon dioxide tension ($Paco_2$), pH and standard base excess (SBE) by means of an automatic blood gas analyser (ABL 2 Radiometer AS, Copenhagen, Denmark). Regional blood flow and cardiac output were determined using the microsphere technique.

The microspheres measuring 15 ± 5 µm were labelled with the gamma emitting nuclides ^{85}St, ^{95}Nb, and ^{141}Ce (3M, Saint Paul, Minnesota, USA) used on three different occasions in an order selected at random to reduce background activity and systematic errors. Fresh pig plasma was added to a suspension of $1.2\text{–}2.0 \cdot 10^6$ microspheres in saline to a total volume of 1 ml and agitated in a Vortex JR mixer. After determination of the isotope activity the microspheres were injected into the left ventricle. During the injection, blood was drawn from the femoral artery into a syringe at a constant rate of 1 ml per min for determination of cardiac output.

A autopsy specimens measuring about 1 cm^3 were taken from the following tissues: lung (two pieces from the apical part of the upper lobe, two pieces from the lower lobe and two pieces from the hilus); heart (two pieces from each ventricle and two from the septum); kidneys (two pieces from each); pancreas and spleen (two pieces from each); liver (five pieces, one from each lobe); biceps muscle of the hind limb (eight pieces); latissimus dorsi muscle (eight pieces); cerebrum (one piece from each hemisphere and one piece from the central part); cerebellum (one piece from each lobe and one from the vermis). The specimens and the reference syringe were analysed in a gamma spectrophotometer (1087, Nuclear, Chicago, IU.) for ^{85}SR-, ^{95}Nb- and ^{141}Ce-activity. The total amount of radioactivity injected was obtained from the activity in the injection syringe before and after microsphere injection.

Experimental protocol

All pigs were normoventilated ($Paco_2$ 5.5 ± 0.2 kPa) during a resting period of 1 h followed either by a two-hour period of hyperventilation to a Pco_2 of 3.0 ± 0.1 kPa or of 2 h of constant normoventilation without change in ventilator settings (Fig. 1).

Group A (n = 10) was studied by microspheres, thermodilution in the pulmonary artery, in six pigs total splanchnic blood flow (ESBF), and femoral artery blood flow. Hyperventilation was induced by increasing tidal volume.

Group AC (n = 6) was studied by thermodilution in the pulmonary artery and femoral arterial blood flow. This group was normoventilated.

Group B (n = 8) was studied by thermodilution in the pulmonary artery and in the portal vein and ESBF by indocyanine extraction. Hyperventilation was, in this group, achieved by increased respiratory frequency.

Group BC (n = 7) was finally studied by the same procedures as in group B. These animals were normoventilated.

Three sets of measurements were performed; immediately before onset of hyperventilation as well as after one and 2 h of hyperventilation or at the corresponding times during normoventilation in the thirteen control animals.

Calculations and statistics

The blood flow to the different organs (*f*) $ml \cdot min^{-1} \cdot g^{-1}$ was calculated as

$$f = \frac{m \cdot fs}{ms}$$

where *m* is the radioactivity in the specimen per gram organ, *ms* the

		Group	Experimental condition		
Hypervent	*n=10*	A	Normovent 60min	Hypervent 120 min	
Controls	*n=6*	AC	Normovent 60min	Normovent 120 min	
Hypervent	*n=8*	B	Normovent 60min	Hypervent 120 min	Normovent 60min
Controls	*n=7*	BC	Normovent 60min	Normovent 120 min	Normovent 60min

Fig. 1. Experimental protocol and number of animals in each group. Group B and BC underwent laparotomy. Hyperventilation in group A was achieved by increasing the tidal volume, while in group B hyperventilation was performed by increasing the respiratory frequency while keeping the tidal volume constant.

radioactivity in the reference syringe and fs the blood sampling rate. Cardiac output was also calculated from the microsphere sample, the factor m here representing the amount of radioactivity injected.

The mean and standard error of the s.e. mean are used in the presentation of data and statistics. An analysis of variance for repeated measurements followed by tests for comparisons between groups ANOVA with Scheffe's F procedure, Fisher's PLSD and the Bonferroni/Dunn procedure were employed for determination of statistic differences. P less than 0.05 was considered significant.

RESULTS

During normoventilation the heart rate in the pigs in group A was 155 ± 9 min^{-1} and tended to decrease ($P > 0.05$). The normoventilated pigs in group AC (n = 6) started with a cardiac output of 184 ± 11 ml · min^{-1} · kg^{-1}, no significant change occurred during the observation period, and after 2 h on ventilator they had a cardiac output of 178 ± 11 ml · min^{-1} · kg^{-1} and after 3 h cardiac output was 183 ± 8 ml · min^{-1} · kg^{-1} (Table 1). The difference between the hyperventilated (A) and the control animals (AC) was significant ($P = 0.024$). Peripheral arterial blood flow measured in femoral artery also differed significantly between the normo (AC) and the hyperventilated groups (A) (Table 1). Group A decreased in femoral artery blood flow measured electromagnetically to 62% ($P = 0.0096$) of initial during the first hyperventilation hour, after which the flow increased slightly to 75% ($P = 0.0186$), while the animals in group AC did not change their femoral flow significantly, either at 2 h (100% of initial) or after 3 h of mechanical ventilation and anaesthesia (90% of initial) (Table 1).

The normoventilated pigs in group AC did not change significantly in MAP, MPAP, MRAP or MPAOP over the 3 h observation.

In group A mean arterial pressure (MAP) and mean pulmonary arterial pressure (MPAP) decreased by 31% and 22%, respectively. The mean right atrial pressure (MRAP) increased from 2.0 ± 0.5 mmHg to 3.5 ± 0.7 mmHg ($P = 0.045$) and mean pulmonary artery occlusion pressure (MPAOP) tended to rise. Systemic vascular resistance (SVR) was 31 ± 4 mmHg · l^{-1} · min^{-1} at normoventilation, no change after 1 h of hyperventilation (31 ± 5 mmHg · l^{-1} · min^{-1}) and a decrease to 25 ± 4 ($P = 0.042$) mmHg · l^{-1} · min^{-1} after 2 h. The pulmonary vascular resistance (PVR) in these pigs did not change significantly. At normoventilation PVR was 4 ± 2 mmHg · l^{-1} · min^{-1}, at 1 h of hyperventilation 3 ± 1 mmHg · l^{-1} · min^{-1} and at 2 h 3 ± 1 mmHg · l^{-1} · min^{-1}.

In group A hyperventilation and the ensuing hypocarbia reduced the blood supply significantly ($P < 0.0001$) to the right ventricle wall, septum and left ventricle wall by 50%, 44%, and 44%, respectively (Fig. 2). The perfusion of lung tissue was not altered during hyperventilation, whereas a significant decrease ($P = 0.0069$) was observed in the spleen at 180 min (Fig. 2). A decrease of blood flow in the kidney was also recorded at the end of the hyperventilation period ($P = 0.0303$) to 28% of that during normoventilation (Fig. 2). The pancreas and the liver blood flow was not significantly affected by hyperventilation as measured by the microsphere method. A marked gradual decrease in muscle blood flow was registered (in the longissimus dorsi muscle to 57% ($P = 0.0163$) and in the biceps muscle to 50% ($P = 0.0036$) of baseline values at the end of the second h of hyperventilation (Fig. 2). Cerebral blood flow also decreased ($P = 0.0011$) by 33% during the last 60 min of hyperventilation. The cerebellar blood flow diminished during

Table 1

Average estimated splanchnic blood flow (ESBF), portal venous blood flow, cardiac output and femoral artery blood flow ± standard error in low frequency high tidal volume hyperventilated pigs (group A), normoventilated pigs (group AC and group BC) and higher frequency with constant tidal volume (group B), data presented for time points after 1, 2, 3, and, for the animals who underwent laparotomy (B and BC), 4 h. All flows presented in ml · min^{-1} · kg^{-1}. Significant difference compared to first normoventilation measurement is marked with an asterisk (*), significant difference to control is marked with an †.

Blood flow	Group	*Ventilation*	60 min	120 min	180 min	240 min
CO thermo	**A**	*hyper 10*	145 ± 10	114 ± 8*	115 ± 9*	†
CO msph	**A**	*hyper 10*	141 ± 7	112 ± 9*	95 ± 10*	
CO thermo	**BC**	*normo 7*	126 ± 14	136 ± 20	162 ± 36	194 ± 27*
CO thermo	**B**	*hyper 8*	139 ± 10	140 ± 12	159 ± 5	182 ± 12*
CO thermo	**AC**	*normo 6*	184 ± 11	178 ± 11	183 ± 8	
ESBF	**BC**	*normo 7*	52 ± 6	49 ± 11	64 ± 13	60 ± 12
ESBF	**B**	*hyper 8*	52 ± 6	53 ± 6	61 ± 4	70 ± 6*
ESBF	**A**	*hyper 6*	53 ± 7	44 ± 7*	41 ± 7*	
Portal	**BC**	*normo 7*	48 ± 7	42 ± 5	44 ± 7	48 ± 7
Portal	**B**	*hyper 8*	59 ± 6	47 ± 5	55 ± 7	61 ± 7
Femoral artery	**AC**	*normo 6*	4.6 ± 0.8	4.6 ± 0.7	4.2 ± 0.7	
Femoral artery	**A**	*hyper 6*	3.9 ± 0.3	2.4 ± 0.2*	2.9 ± 0.3*	†

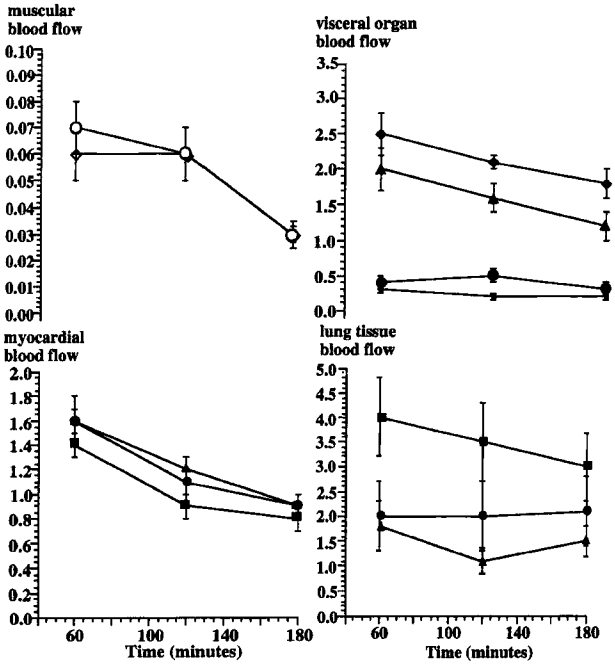

Fig. 2. Organ blood flows per gram tissue in: *Upper left:* skeletal muscle; biceps (-◇-) and longissimus dorsi (-○-), *upper right:* visceral organs; liver (-•-), pancreas (-●-), spleen (-▲-) and kidney (-◆-), *lower left:* myocardial; right ventricle (-■-), septum (-●-) and left ventricle (-▲-) and *lower right;* pulmonary tissue; hilus (-■-), base (-●-) and apex (-▲-), all in ml · min^{-1} · g^{-1} ± s.e. mean as a function of time. The first measurement was done during normoventilation (60 min), the following two during hyperventilation (120 and 180 min), low frequency high tidal volume (group A).

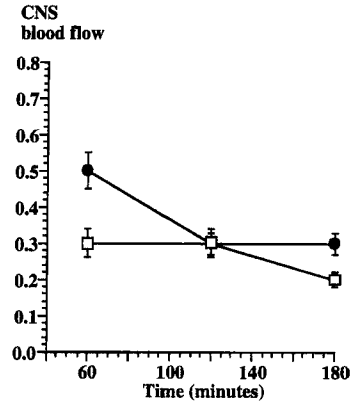

Fig. 3. Cerebral (-□-) and cerebellar (-●-) blood flows per gram tissue in ml · min^{-1} · g^{-1} ± s.e. mean as functions of time in the low frequency high tidal volume animals (group A). At 60 min the animals are normoventilated, at 120 and 180 min they are hyperventilated.

the first 60 min ($P=0.0143$) of hyperventilation (−40%), but seemed to stabilise later on (Fig. 3).

Cardiac output (CO) measured by microspheres correlated closely to the values obtained by thermodilution. Considering all observations independent, although they were three from each animal, the line had an $r^2=0.705$, and the equation for the regression line:

$$CO_{microspheres} = 0.291 + 0.817 \cdot CO_{thermodilution}$$

In the group B cardiac output did not change during hyperventilation; 139 ± 10 ml · min^{-1} · kg^{-1} during normoventilation, 140 ± 12 ml · min^{-1} · kg^{-1} at 60 min and 159 ± 5 ml · min^{-1} · kg^{-1} at 120 min of hyperventilation, respectively, expressed as cardiac output per kg body mass (Table 1). MAP and MPAP did not show any significant changes during hyperventilation. However, MRAP gradually increased from 5.0 ± 0.4 mmHg to 7.6 ± 0.4 mmHg ($P=0.0004$), and mean pulmonary artery occlusion pressure (MPAOP) from 5.9 ± 0.8 mmHg to 8.5 ± 0.9 mmHg ($P=0.0017$) after 2 h of hyperventilation, followed by a reduction to 6.6 ± 0.9 mmHg when the normoventilation was reinstated. The blood flow in the portal vein tended to decrease from 59 ± 6 ml · min^{-1} · kg^{-1} to 47 ± 5 ml · min^{-1} · kg^{-1} ($P=0.17$) and 60 and 55 ± 7 ml · min^{-1} · kg^{-1} at 120 min of hyperventilation expressed as flow per kg body mass (Table 1), at the control period after hyperventilation the portal blood flow was 61 ± 7 ml · min^{-1} · kg^{-1}. The control group BC had a portal blood flow of 48 ± 7 ml · min^{-1} · kg^{-1}, 42 ± 5 ml · min^{-1} · kg^{-1}, 44 ± 7 ml · min^{-1} · kg^{-1}, 48 ± 7 ml · min^{-1} · kg^{-1} at the respective times. The estimated total splanchnic blood flow, ESBF, in group A decreased, at first measurement it was 53 ± 7 ml · min^{-1} · kg^{-1}, decreased to 44 ± 7 ml · min^{-1} · kg^{-1} ($P=0.0138$) after 1 h of hyperventilation and remained at the same level, 41 ± 7 ml · min^{-1} · kg^{-1} after 2 hyperventilation h ($P=0.0047$). ESBF in group B as well as in group BC underwent no significant change over time. Compared to first control the SVR did not increase significantly during hyperventilation in the group B. The first control measurement of SVR was 27 ± 2 mmHg · l^{-1} · min^{-1}, after 1 h of hyperventilation it was 30 ± 2 mmHg · l · min^{-1}, at 2 h 29 ± 1 mmHg · l^{-1} · min^{-1} and at the second normocapnic control it was 26 ± 2. The decrease from two h of hyperventilation to second control was significant ($P<0.05$). The PVR was at control 12 ± 1 mmHg · l^{-1} · min^{-1}, after 1 h of hyperventilation 10 ± 1 mmHg · l^{-1} · min^{-1}, after 2 h 11 ± 1 mmHg · l^{-1} · min^{-1}. At the second control it was 17 ± 1 mmHg · l^{-1} · min^{-1}, the difference between the 2 hyperventilation measurements and the second control being significant ($P<0.0001$).

DISCUSSION

Passive hyperventilation during anaesthesia using intermittent positive pressure ventilation may affect vas-

cular resistance, and, because of this, systemic circulation and tissue perfusion, due to the reduction in carbon dioxide tension resulting in hypocapnic alkalosis, and by direct actions on the myocardial performance. Unilateral hyperinflation of the lungs in dogs produces a vagally mediated reflex depression of both right and left ventricular performance (18). In the present study hyperventilation with the ventilation frequency of 20 min^{-1} induced a significant decrease in cardiac output in this group of animals as measured by both the thermodilution and the microsphere techniques. To elucidate the effect of different tidal volumes on cardiac output hypocarbia was induced by increasing the ventilator frequency from twenty breaths to forty breaths min^{-1} in eight of the pigs. In the constant frequency group (A) cardiac output fell by 21% while it remained unchanged compared to normoventilation in the pigs ventilated with the higher frequency (group B). This was possibly induced by a higher mean intrathoracic pressure and thereby a reduced venous return in group A (19). Thus, MRAP measured during ventilation, increased during hyperventilation in both groups, possibly depending on an increase in the intrathoracic pressure when hyperventilation was induced. There was a statistically significant increase in MPA-OP after 2 hours of hyperventilation in the low frequency group (A). The concomitant reduction in MPAP suggests a possible reduction in right myocardial performance or an effect on pulmonary vascular resistance (7, 20).

The normoventilated control animals presented did not show any significant change over time in circulatory pressures, cardiac output or femoral arterial blood flow. The changes in circulation inflicted on them by general anaesthesia and mechanical ventilation seemed to be completed at the first observation point and constant over time. The microsphere pigs did not have any other control than the first observation point during normoventilation. Pigs normoventilated with or without laparotomy remained in the same circulatory state over the whole observation period, both considering central haemodynamics, ESBF, portal flow and femoral artery blood flow. We find it perfectly feasible, judged from our own data here presented, to draw the conclusion that the major changes in circulation taking place after the addition of hyperventilation and the ensuing hypocapnia in our pig model are caused by the hyperventilation and not by ventilation or anaesthesia *per se*.

In the present study we observed that the values on portal vein flow obtained was sometimes higher than the estimated total splanchnic blood flow. This is in line with an observation in our laboratory of a higher estimation of the portal blood flow with thermodilution as compared to transit time ultrasound flowmetry (21) by over 20% when flow is around 1 $l \cdot min^{-1}$ and even more below. Hartman and co-workers (22) have demonstrated that compared to the actual flow derived by measurement of the outflow from an artery even transit time ultrasound measurements overestimated the actual flow by 2 to 6%. Furthermore indocyanine estimation of flow has a time constant much longer than thermodilution, as the infusion was going over a time of 20 to 30 min while in thermodilution all measurements are concluded in a few minutes. This explains why our data, here presented without corrections for known methodological errors, can give higher figures for the portal venous blood flow compared to the total splanchnic blood flow.

The pulmonary vascular resistance tended to decrease in both groups of hyperventilated animals, while it remained constant in the normoventilated pigs, this effect was probably more pH-related than related to the actual P_{CO_2}-value (23). During hyperventilation myocardial blood flow in the group A decreased in both the right and left ventricle walls as well as in the septum comparable to the situation in humans (24). Neill and Hattenhauer's (24) finding of a decrease in myocardial O_2 supply during hypocarbia by voluntary hyperventilation excludes the influence of an increase in intrathoracic pressure interacting with central circulation. It has also been demonstrated (9) that induction of hypocarbia by hyperventilation, during intermittent positive pressure ventilation with constant tidal volumes and frequency, reduces myocardial blood flow. Hyperinflation of the lungs together with hypocarbia or the resulting pH-change may act synergistically to reduce myocardial blood flow. Using tidal volumes resulting in hyperventilation all over the experiment and adding CO_2 to inspiratory gas, Semb et al. (9) were able to show that myocardial and cerebral flow increased during hypercarbia and decreased during hypocarbia. Hypocarbia alone increased blood flow in the liver, kidneys and skeletal muscle. Our finding of a decrease in blood flow in these organs during hypocarbia due to hyperventilation (group A), as compared to during normoventilation, seems contrary to Semb's findings, but may partly be explained by the decrease in cardiac output in the low frequency group. In the animals hyperventilated with constant tidal volume (group B) the systemic vascular resistance showed a tendency to increase during hyperventilation, this reverting to normal when normocapnia was reinstated, an effect that we consider directly related to the P_{aCO_2}-change or the parallel pH-shift. The skeletal muscle blood flow was reduced by more than 50% in the present study during hyperventilation with high tidal volume, which might lead to an insufficient blood

flow to the skeletal muscles of the leg. In the same direction as the microsphere results points the result of the femoral artery blood flow measurements, which indicated a reduction in flow of almost 40% early during hyperventilation. These data necessitate investigation of substrate availability and oxygen transport to skeletal muscle tissues during hyperventilation.

As expected (25), cerebral blood flow was reduced by more than 30% during hypocarbia in the group A animals in the present study. Normocapnic IPPV with a positive end-expiratory pressure (PEEP) of 8 cmH_2O (26) reduces cardiac output to the same extent as in group A in the present hyperventilation study. This possibly indicates that preload is affected to the same extent. However, these authors were unable to detect any changes in cerebral blood flow. At a PEEP level of 8 cmH_2O Haldén et al. (26) found a reduction in heart perfusion of 3% compared to the same variable during normoventilation with no PEEP. The cerebellar flow in that study was increased by 20%. Arterial blood flow to the kidneys and skeletal muscle was unchanged, while pancreas and spleen had a flow reduced by 60% and 63%, respectively. These findings are not in agreement with the present results of a reduced arterial blood flow to the cerebellum of 40%, to the kidneys of 28%, to the skeletal muscle of 50%, to the heart muscle of 44 to 50%, while the pancreas and the liver only showed minor changes in flow compared to normoventilation.

Haldén et al. (26) have shown that during IPPV with positive end-expiratory pressure and no significant change in $Paco_2$ "the central organs", heart, kidney and cerebellum, are given priority in the distribution of cardiac output. Our finding of a reduced flow even to these organs raises the hypothesis that $Paco_2$ is the factor responsible for this difference in flow. If considered true, this explanation seems to confirm the decrease in myocardial and cerebral blood flow found by Semb et al. (9) during hypocarbia, and the finding by Neill and Hattenhauer (24) of a decreased myocardial oxygen supply during voluntary hyperventilation.

In conclusion, passive mechanical hyperventilation during anaesthesia using intermittent positive pressure ventilation and high tidal volume reduced cardiac output, femoral artery blood flow, estimated total splanchnic blood flow (ESBF) and peripheral tissue blood flow. However, the changes in cardiac output and splanchnic blood flow were not observed when hyperventilation was induced by increased frequency, keeping the tidal volume constant. The observed changes are considered by us to be the effects of the hypocarbia, the ensuing change in pH as well as of the changes in preload.

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REFERENCES

1. Bozza Marrubini M L, Rossanda M, Tretola L. The role of artificial hyperventilation in control of brain tension during neurosurgical operations. *Br J Anaesth* 1961: **36**: 415–421.
2. Gordon E, Rossanda M. Artificial hyperventilation in the treatment of patients with severe brain lesions. In: Brock M, Fieschi C, Ingvar D, et al. eds. Cerebral blood flow. Berlin: Springer-Verlag, 1969: 258–259.
3. Fleckenstein A, Nakayama K, Fleckenstein-Grün G, Byron Y K. Ionic action on vascular smooth muscle. In: Betz E, ed. Symposium on vascular smooth muscles. Berlin: Springer Verlag, 1976: 117–123.
4. Yasue H, Nagao M, Omote S, Takizawa A, Miwa K, Tanaka S. Coronary arterial spasm and Prinzmetal's variant form of angina induced by hyperventilation and Tris-buffer infusion. *Circulation* 1978: **58**: 56–62.
5. Wexels J C. Myocardial oxygen supply during hypocapnia and hypercapnia in the dog. *Can J Physiol Pharmacol* 1986; **64**: 1376–1380.
6. Wexels J C, Myhre E S. Hypocapnia and hypercapnia in the dog: effects on myocardial blood-flow and haemodynamics during beta- and combined alpha- and beta-adrenoceptor blockade. *Clin Physiol* 1987: **7**: 21–33.
7. Morray J P, Lynn A M, Mansfield P B. Effect of pH and Pco_2 on pulmonary and systemic hemodynamics after surgery in children with congenital heart disease and pulmonary hypertension. *J Pediatr* 1988: **113**: 474–479.
8. Price H. Effects of carbon dioxide on the cardiovascular system. *Anesthesiology* 1960: **6**: 652–663.
9. Semb B K, Hysing E, Mörkrid L. Effect of CO_2 on peripheral flow and central hemodynamics. *Eur Surg Res* 1984: **2**: 133–139.
10. Prys-Roberts C, Kelman G R, Greenbaum R, Kain M L, Bay J. Hemodynamics and alveolar-arterial PO_2 difference at varying $Paco_2$ in anesthesized man. *J Appl Physiol* 1968: **25**: 80–87.
11. Cullen D, Eger E. Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974: **41**: 345–349.
12. Johnson E E. Splanchnic hemodynamic response to passive hyperventilation. *J Appl Physiol* 1975: **38**: 156–162.
13. Bradley S E, Ingelfinger F J, Bradley G P, Curry J J. The estimation of hepatic flow in man. *J Clin Invest* 1945: **24**: 890–897.
14. Caesar J, Shaldon L, Chiandussi, Guevara L, Sheila S. The use of indocyanine green in the measurement of hepatic blood flow and as test of hepatic function. *Clin Sci* 1961: **21**: 43–57.
15. Garby L, Vuille J C. The amount of trapped plasma in a high speed microcapillary hematocrit centrifuge. *Scand J Clin Lab Invest* 1961: **13**: 642–645.
16. Bradley E L. Measurement of hepatic blood flow in man. *Surgery* 1974: **75**: 783–789.
17. Perry M A, Parker J C. Indicator dilution measurements of splanchnic blood flow. in: Granger D, Buckley G B, ed. Measurement of blood flow applications to the splanchnic circulation. Baltimore: Williams & Wilkins, 1981: 161–176.
18. Cassidy S, Eschenbacher W L, Johnson R L. Reflex cardiovascular depression during unilateral lung hyper inflation in the dog. *J Clin Invest* 1979: **64**: 620–626.
19. Venus B, Cohen L E, Smith R A. Hemodynamics and intrathoracic pressure transmission during controlled mechanical venti-

lation and positive end-expiratory pressure in normal and low compliant lungs. *Crit Care Med* 1988: **16**: 686–690.
20. Lyrene R K, Welch K A, Godoy G, Philips J. Alkalosis attenuates hypoxic pulmonary vasoconstriction in neonatal lambs. *Pediatr Res* 1985: **19**: 1268–1271.
21. Rubertsson S, Arvidsson D, Wiklund L, Haglund U. Comparison of blood flow measurement in the portal vein and pulmonary artery using transit-time ultrasound flowmetry and thermodilution techniques. *Surg Research Comm* 1993: **13**: 309–316.
22. Hartman J, Koerner J, Lancaster L, Gorczynski R. In vivo calibration of a transit time ultrasound system for measuring ascending aorta volume flow. *The Pharmacologist* 1985: **27**: 217.
23. Schreiber M D, Heymann M A, Soifer S J. Increased arterial pH, not decreased $Paco_2$, attenuates hypoxia-induced pulmonary vasoconstriction in newborn lambs. *Pediatr Res* 1986: **20**: 113–117.
24. Neill W A, Hattenhauer M. Impairment of myocardial O_2 supply due to hyperventilation. *Circulation* 1975: **52**: 854–858.
25. Miyazaki M. Circulatory effect of respiratory maneuvers. *Angiology* 1978: **29**: 541–547.
26. Haldén E, Jakobson S, Janerås L, Norlén K. Effects of positive end-expiratory pressure on cardiac output distribution in the pig. *Acta Anaesthesiol Scand* 1982: **26**: 403–408.

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