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Effects of arterial carbon dioxide manipulation on cerebral oxidative metabolism during hemorrhagic hypotension in dogs

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Summary

Background. Development of brain acidosis is concerned during prolonged hemorrhagic hypotension due to blood-brain barrier disruption, even though cerebral blood flow is maintained. There is possibility that $PaCO_2$ manipulation affects brain acidosis induced deterioration of cerebral oxidative metabolism by influencing the brain acid-base equilibrium.

Methods. A dog model of hemorrhagic hypotension was used. Mean arterial pressure was kept at the lower limit of autoregulation to assure maintained cerebral blood flow. One of three different $PaCO_2$ manipulations, hypocapnia, normocapnia or hypercapnia, was applied during hypotension and the effect of $PaCO_2$ manipulations on cerebral oxidative metabolism was estimated.

Results. Cerebral blood flow and cerebral metabolic rate for oxygen remained unaltered during hypotension. Brain acidosis was developed regardless of the $PaCO_2$ manipulation used, being most acidotic with hypercapnia. Hypercapnia was accompanied by a significant decrease in phosphocreatinine and an increase in the L/P ratio compared to hypocapnia and normocapnia.

Conclusions. $PaCO_2$ manipulation differentially affects cerebral oxidative metabolism during hemorrhagic hypotension with preserved cerebral blood flow, being worse with hypercapnia.

Keywords: hemorrhagic hypotension, brain acidosis, cerebral oxidative metabolism, $PaCO_2$

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Introduction

Severe hypotension due to hemorrhage is a pathological condition that occurs frequently in the clinical practice of anesthesia. Hemorrhagic hypotension causes redistribution of blood flow to important organs like heart and brain at the expense of other tissues[1]. This compensatory mechanism leads to systemic lactic acidosis, while cerebral blood flow (CBF) is maintained insofar as mean arterial pressure (MAP) is kept above the lower limit of autoregulation (LLA)[2]. Because permeability of the blood-brain barrier (BBB) to hydrogen ions is low[3,4], it is unlikely that systemic acidosis directly influences on the brain acid-base equilibrium. However, prolonged hemorrhagic hypotension, MAP 40 mmHg for >20 min, has been shown to cause BBB dysfunction to increase permeability[4]. Therefore, development of brain acidosis by transmitted hydrogen ions from circulating blood, is concerned when hemorrhagic hypotension persists, even though CBF is maintained.

Brain acidosis promotes the release of Ca^{2+} from intracellular stores to increase intracellular Ca^{2+}, which impairs mitochondrial function to deteriorate ATP-generative pathway of oxidative phosphorylation or cerebral oxidative metabolism[5]. Because carbon dioxide easily passes through the BBB and penetrates cerebral vessel smooth muscles[3], there is possibility that $PaCO_2$ manipulation alters the brain acid-base equilibrium and thus influence on cerebral oxidative metabolism in this clinical situation. However, this issue has not been investigated. Clarifying the effect of $PaCO_2$ manipulation on cerebral oxidative metabolism during hemorrhagic hypotension is of clinical importance as it serves target ventilatory mode during anesthetic management.

Accordingly, we examined this issue by using a dog model of hemorrhagic hypotension with maintained CBF. Maintenance of CBF as a control value was assured by keeping MAP at the LLA level during the hypotensive period. This protocol also eliminated the confounding factor of carbon dioxide reactivity of CBF and allowed us to observe only the $PaCO_2$ effect on cerebral oxidative metabolism. One of three $PaCO_2$ conditions, hypocapnia, normocapnia, or hypercapnia, was applied during hemorrhagic hypotension and cerebral oxidative metabolism related measurements were performed. We hypothesized that hypocapnia would prevent further deterioration of cerebral oxidative metabolism compared to other $PaCO_2$ conditions by counteracting brain acidosis progression.

Methods

Approval for our animal study was obtained from the Institutional Animal Laboratory Committee of Yamagata University School of Medicine. Twenty male mongrel dogs, weighing between 9.0 and 13.2 kg (with a mean body weight of 11.2 kg) were enrolled in the study. Dogs were made to fast over night, but were allowed free access to water. Anesthesia was induced with an intravenous bolus dose of 5 mg kg^{-1} ketamine along with 0.2 mg kg^{-1} pancuronium to facilitate tracheal intubation. Anesthesia was maintained throughout the procedure with a continuous infusion of ketamine at the rate of 2 mg kg^{-1} h^{-1} and pancuronium at 0.1 mg kg^{-1} h^{-1}. After tracheal intubation, the lungs were mechanically ventilated, the minute ventilation being adjusted

to maintain $PaCO_2$ at 20 mmHg. Carbon dioxide was externally added to the anesthesia circuit to maintain the $PaCO_2$ between 35 and 40 mmHg during surgical preparation. The fraction of inspired oxygen was maintained at 1.0 throughout the study. Esophageal temperature was maintained between 37.5 and 38.5°C by servoregulation using a heating pad. A bilateral cortical electroencephalogram (EEG) was monitored via electrodes inserted onto the frontal and parietal bones. Lactated Ringer's solution, 5 ml kg^{-1} h^{-1}, was infused to provide maintenance fluid requirements.

Under aseptic precautions, all surgical fields were carefully infiltrated with 1% lidocaine. With the animal in the supine position, the femoral artery was cannulated for blood pressure measurement and arterial blood sampling. Both femoral veins were cannulated for drug administration and for blood withdrawal for the induction and maintenance of hemorrhagic hypotension. The animal was then turned prone and placed in the sphinx position with the head fixed in a stereotaxic frame. The scalp was incised and a burr hole ~1 cm in diameter was drilled in the skull above the left frontal cortex, for later sampling of brain tissue. The dura was left intact. A venous outflow technique was used to measure CBF. After the sagittal sinus was exposed, a tapered catheter (2 mm internal diameter) was passed 2-4 mm anteriorly into the posterior sagittal sinus, blood from here being returned to the external jugular vein via an electromagnetic flow probe[6]. The site of cannulation was packed with Surgicel®. Heparin, 1 mg kg^{-1}, was administered prior to sinus cannulation, and the same dose was repeated hourly. Following surgical preparation, a 30-min interval was allowed for physiological stabilisation.

Prior to the main study, a pilot study was performed with four animals to determine the LLA under these surgical conditions under normocapnia. MAP was decreased in a stepwise fashion from 60 mmHg to 30 mmHg by exsanguination via the femoral venous catheter. CBF reduction was observed when MAP was decreased to below 40 mmHg. Further reduction of MAP was related to unstable hemodynamics. A MAP of 40 mmHg was therefore considered appropriate to balance the hemorrhagic insult and animal tolerance, and the value was adopted as the LLA in our experiment.

After stabilisation, animals were randomly assigned to one of the three pre-determined $PaCO_2$ manipulation groups: P20G (n = 7) as the hypocapnia group, in which $PaCO_2$ was maintained at 20 mmHg; P40G (n = 7) as the normocapnia group, in which $PaCO_2$ was maintained at 40 mmHg; and P80G (n = 6) as the hypercapnia group, with a $PaCO_2$ at 80 mmHg. In P20G, supplemental carbon dioxide was terminated. The carbon dioxide flow was regulated to maintain the $PaCO_2$ at 40 mmHg and 80 mmHg for P40G and P80G groups, respectively. Following an additional 30-min stabilisation period, blood was withdrawn via the femoral venous catheter and the MAP was lowered to 40 mmHg over 10 min and maintained at this level for 60 min. The amount of blood withdrawn was 57 ± 10 ml kg^{-1}, 59 ± 14 ml kg^{-1}, and 49 ± 7 ml kg^{-1} for P20G, P40G and P80G, respectively (P=0.193). $PaCO_2$ conditions in each group were rigidly maintained throughout the experimental period by intermittent blood gas analyses. Physiological parameters, CBF, and cerebral metabolic rate for oxygen ($CMRO_2$) were measured at two

time points: at the end of the first stabilisation period and before group assignment (control values), and after 60 min of hemorrhagic hypotension (shock values). Sagittal sinus blood was sampled for control and shock values, and served as an indicator for brain acidosis.

CBF measurements were made using electromagnetic probe readings and expressed as ml min^{-1}, due to technical difficulties associated with dye injection studies required to express values as ml 100 g^{-1} min^{-1}. The venous outflow technique represents anterior and superior surfaces of both cerebral hemispheres, the weight of the brain drained by the sagittal sinus being reported as 43 - 48% of the total brain weight in the dog[6,7]. $CMRO_2$ was calculated as:

$CMRO_2 = CBF\ (CaO_2\text{-}CsO_2)/100$,

where CaO_2: arterial oxygen content and CsO_2: sagittal sinus oxygen content. The value was divided by 100 to match the system of units of CBF, being expressed as ml min^{-1}.

At the end of 60 min of the hemorrhagic state, the dura overlying the cerebral hemispheres was excised, and approximately 1 g of cortical brain tissue was taken into liquid nitrogen within 1 s. Animals were euthanized with high dose halothane administration. Brain tissue samples were stored at -76°C for less than 12 h, then prepared for analyses in a refrigerated chamber at -25°C. Glycolytic intermediates and high-energy phosphate reserves, including phosphocreatinine (Pcr), in the brain were determined fluorometrically using pyridine nucleotides and appropriate enzymes. The L/P ratio was calculated from lactate and pyruvate values. The energy state of the brain tissue was expressed as the energy charge (EC) of the adenine pool[8]:

EC = ([ATP] + [ADP]/2)/([ATP] + [ADP] + [AMP])

Statistical analysis

Statistical analysis was performed by means of a JMP® 5.0 software package (SAS Institute Japan). Data are presented as mean ± SD. We used a non-parametric test in this study due to the number of animals used, and the violation of normality in some variables. Values were analysed with the Kruskal-Wallis test. If statistical differences were detected, the Mann-Whitney-Wilcoxon test was used for intergroup comparisons. Comparisons between control and shock values were assessed by the Mann-Whitney-Wilcoxon test, except for MAP, hematocrit, and $PaCO_2$. Differences were considered significant if $P < 0.05$.

Results

Esophageal temperature was tightly controlled throughout the experiment in all animals. EEG was also attenuated during hemorrhagic hypotension in all animals.

Table 1 shows the physiological variables, CBF, and $CMRO_2$ in the three groups. Under control conditions and before induction of hemorrhagic hypotension, there were no statistically significant differences between groups in any of the variables.

With shock, the intended $PaCO_2$ levels could be achieved in the respective groups. MAP, hematocrit, and PaO_2 were not different between groups. Heart rate in P20G was significantly higher compared to the other groups. Serum glucose was significantly elevated in all groups with no intergroup differences. Arterial pH was preserved in P20G, while decreasing in the other groups, with P80G

being most acidotic. Base excess significantly decreased in all groups with P80G being most acidotic. Sagittal sinus pH also significantly decreased in all groups with P80G being most acidotic.

CBF and $CMRO_2$ were similar at control among groups. Hemorrhagic hypotension did not significantly alter these values within each group. However, at shock, animals in the P80G had significantly higher CBF and $CMRO_2$ compared to P20G, P40G, and P20G, respectively. The figure summarises the changes in CBF and $CMRO_2$.

Table 2 shows the cerebral oxidative me-

Table 1. Physiological variables under control and shock conditions. Data are expressed as mean ±SD.

	P20G	P40G	P80G
Body weight (kg)	11.4 ± 1.1	11.4 ± 1.2	10.6 ± 1.1
Control			
Heart rate	203.3 ± 40.6	188.6 ± 38.9	169.0 ± 38.5
MAP (mmHg)	155.3 ± 26.9	156.6 ± 31.8	152.2 ± 19.3
Hematocrit (%)	45.4 ± 6.3	47.3 ± 4.6	44.3 ± 4.8
Esophageal temperature (°C)	38.0 ± 0.4	38.1 ± 0.5	38.2 ± 0.2
Arterial pH	7.315 ± 0.02	7.289 ± 0.05	7.328 ± 0.03
Arterial base excess	-3.7 ± 1.4	-4.6 ± 2.4	-3.1 ± 1.4
$PaCO_2$ (mmHg)	41.6 ± 3.5	42.0 ± 2.2	40.7 ± 1.6
PaO_2 (mmHg)	578.3 ± 35.6	578.7 ± 19.6	590.5 ± 27.0
Sagittal sinus pH	7.254 ± 0.02	7.235 ± 0.04	7.259 ± 0.03
Glucose (mg dl^{-1})	157.6 ± 20.0	156.3 ± 20.0	161.8 ± 21.6
CBF (ml min^{-1})	28.0 ± 8.4	24.4 ± 9.8	28.3 ± 7.4
$CMRO_2$ (ml min^{-1})	1.63 ± 0.46	1.49 ± 0.42	1.78 ± 0.41
Shock			
Heart rate	248.6 ± 28.0 #a	209.0 ± 22.0	204.5 ± 32.6
MAP (mmHg)	39.7 ± 1.4	38.3 ± 2.4	37.7 ± 1.5
Hematocrit (%)	17.8 ± 3.6	23.6 ± 4.6	25.6 ± 7.2
Esophageal temperature (°C)	38.4 ± 0.3	38.3 ± 0.6	38.0 ± 0.4
Arterial pH	7.273 ± 0.11	7.141 ± 0.01 #	6.812 ± 0.05 #b,c
Base excess	-16.9 ± 5.0 #	-15.2 ± 5.3 #	-26.0 ± 3.1 #c
$PaCO_2$ (mmHg)	17.6 ± 2.4	41.7 ± 4.2	86.7 ± 4.2
PaO_2 (mmHg)	595.0 ± 41.8	567.3 ± 34.4	540.7 ± 21.0
Sagittal sinus blood pH	7.116 ± 0.11 #	7.031 ± 0.10 #	6.736 ± 0.05 #b,c
Glucose (mg dl^{-1})	460.1 ± 56.0 #	271.6 ± 56.0 #	379.3 ± 60.5 #
CBF (ml min^{-1})	22.3 ± 7.5	18.6 ± 2.7	33.3 ± 7.6 #
$CMRO_2$ (ml min^{-1})	1.64 ± 0.44	1.45 ± 0.18	2.05 ± 0.26 #

a significant difference compared with P20G and P40G.
b significant difference compared with P20G and P80G.
c significant difference compared with P40G and P80G.
significant difference between control and shock conditions.

tabolism-related variables sampled at the end of 60 min of hemorrhagic shock. Brain ATP, ADP, AMP and lactate were not significantly different among the groups. However, in P80G, Pcr was significantly lower and the L/P ratio was higher compared to the other groups. EC was not significantly different among the groups.

Discussion

In the present study, $PaCO_2$ manipulation differentially influenced both arterial and sagittal sinus blood pH, and heart rate. Arterial pH was preserved in P20G, and decreased in P40G and P80G. Judging by base excess of arterial blood, the severity of systemic acidosis was similar in both P20G and P40G. Sagittal sinus blood pH significantly decreased in all groups, being most acidotic in P80G. Heart rate was significantly higher in P20G as compared to the other groups. The mechanisms for this tachycardic reaction are unclear, although hypocapnia induced circulatory depression may have been responsible[9]. Hyperglycemia developed in all groups during shock, with most evident in P20G and moderate in P40G, however, intergroup differences were not significant (P = 0.064). The development of marked hyperglycemia suggests the activation of the adreno-sympathetic system.

The target MAP for exsanguination was set at the LLA level so that the effects of carbon dioxide reactivity on CBF were eliminated

Table 2. Cerebral oxidative metabolism-related variables.

	ATP (μmol g^{-1})	ADP (μmol g^{-1})	AMP (μmol g^{-1})	Pcr (μmol g^{-1})	EC	Lactate (μmol g^{-1})	L/P ratio
P20G	1.34 ± 0.23	0.39 ± 0.11	0.12 ± 0.06	2.28 ± 0.44	0.83 ± 0.04	7.00 ± 2.51	37.8 ± 11.4
P40G	1.30 ± 0.24	0.33 ± 0.80	0.10 ± 0.04	2.15 ± 0.34	0.85 ± 0.02	4.40 ± 2.26	36.4 ± 15.3
P80G	1.17 ± 2.30	0.49 ± 0.14	0.23 ± 0.18	1.39 ± 0.35 *	0.76 ± 0.10	5.19 ± 3.06	65.9 ± 20.8 *

*: significant difference compared with P20G and P40G.
ATP: adenosine triphosphate, ADP: adenosine diphosphate, AMP: adenosine monophosphate, Pcr: phosphocreatinine, EC: electrical charge potential, L/P ratio: lactate and pyruvate ratio

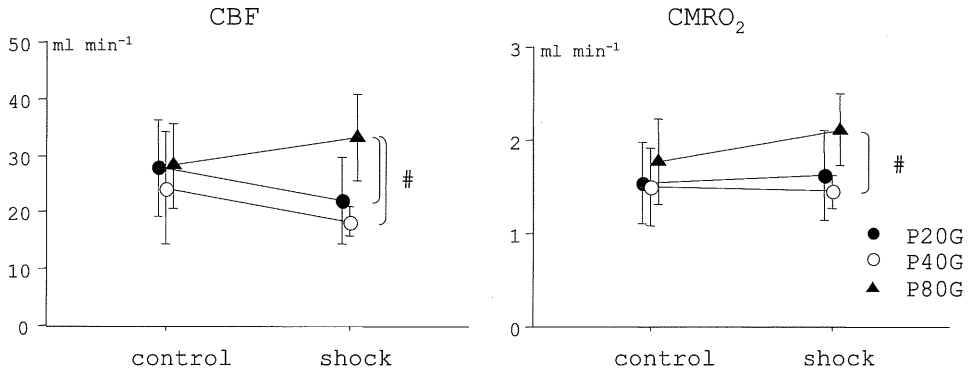

Figure. Changes in CBF and $CMRO_2$ during control and shock conditions.
CBF and $CMRO_2$ were not significantly altered during 60 min of hemorrhagic hypotension in all groups. With shock, CBF was significantly higher in P80G compared to P20G and P40G, and $CMRO_2$ was significantly higher in P80G compared to P40G.
#: significant difference among groups

and only $PaCO_2$ effects on cerebral oxidative metabolism were evident. The MAP value for LLA was determined by a pilot study under normocapnic conditions. However, carbon dioxide reactivity could not be fully excluded in P80G, in which CBF and $CMRO_2$ were significantly higher at shock compared to the other groups. A MAP of 40 mmHg being the LLA concurs with other study using similar hemorrhagic hypotension model[10], being different, however, from other model using pharmacological hypotension, in which the LLA was 60% of cerebral perfusion pressure or a MAP of 50 mmHg[7]. In the pharmacological hypotension model, contrary to our model, acidosis was absent both in arterial and sagittal sinus blood and EEG attenuation was not observed. We assume that activated adreno-sympathetic system in our model might have resulted in substantial vasoconstriction and thus the LLA was shifted to the left.

During 60 min of hemorrhagic hypotension, brain acidosis was developed in all groups, as indicated by decreased sagittal sinus blood pH and increased level of brain lactate and L/P ratio, the normal values of which are reported to be 1.23 ± 0.04 μmol g^{-1} and 11 ± 0, respectively[11]. We surmised that the etiologies of brain acidosis included two mechanisms. One was the transition of hydrogen ions from circulating blood through the disrupted BBB[4]. The other was the lactate production at regionally hypoperfused areas in the brain. It is reported during hemorrhagic hypotension that > 40 ml kg^{-1} of exsanguination causes unequal intracerebral blood flow distribution to result in significant regional variations[12]. Since blood was exsanguinated between 41.5 to 83.3 ml kg^{-1}in our experiment, regional ischemic areas may have been taking place during hemorrhagic hypotension, although CBF were seemingly unchanged. Observed EEG attenuation also supported the existence of ischemic regions. The assumption may also explain the consistently lower sagittal sinus blood pH to that of the arterial.

Brain acidosis is generally a characteristic condition of brain damage with the existence of persistent residual CBF, i.e. incomplete global ischemia and traumatic brain injury[13]. Thus, development of brain acidosis is usually a consequence of brain damage. However, acidosis *per se* is known to damage the brain, as hydrogen ions are harmful to neurons[14,15]. There are several mechanisms proposed regarding acidosis-mediated brain damage, such as the production of reactive oxygen species[16], cellular swelling via impaired activity of volume-sensitive anion channels[17,18], promote the process of apoptosis[19], and intracellular Ca^{2+} increase[5,20]. Increased intracellular Ca^{2+} impairs mitochondrial function, which results in the deterioration of cerebral oxidative metabolism[5].

Among therapeutic interventions to treat brain acidosis, $PaCO_2$ manipulation is thought be simple and potent to influence both the CBF and brain acid-base equilibrium. It has been reported that $PaCO_2$ manipulation may influence neurological outcome under circumstances of traumatic brain injury, in which hypocapnia caused further exacerbation of preexisting impairment of CBF and $CMRO_2$[21], and increased the ischemic brain volume[22]. In patients with brain ischemia, normocapnia is recommended, however, detailed effects of the $PaCO_2$ status on neuronal survival effects have not been elucidated[23]. For the treatment of hemorrhagic hypotension associated brain acidosis, the expected role of $PaCO_2$ manipu-

lation is to modulate the brain acid-base equilibrium and thus improve neuronal environment.

Deterioration of cerebral oxidative metabolism, when associated with brain ischemia, advances gradually. Until moderate ischemia, brain ATP remains unchanged due to the conversion of ADP and Pcr to ATP. Then, Pcr level starts to decrease at severe ischemia. Reduction in brain ATP levels follows, thus, decrease of EC represents a more severe hypoxic state[24]. Ultimately ATP is depleted with complete ischemia[25]. Hence, brain Pcr is considered to be a more sensitive marker of the deterioration of oxidative metabolism than brain ATP[24]. In the present study, concentrations for ATP, ADP, AMP, EC, and lactate were similar among the groups. Pcr was significantly decreased and L/P ratio was significantly increased in P80G, whereas, P20G and P40G had similar values. When referring to the relationship of ischemia-related cerebral oxidative metabolism deterioration, reduction of Pcr in P80G indicates the occurrence of moderate to severe ischemia equivalent insult, although CBF was higher compared to the other groups. An increased L/P ratio also indicates the exacerbation of anaerobic metabolism. The effects of hypocapnia and normocapnia on cerebral oxidative metabolism were similar. Since our study was conducted under conditions of acute hemorrhagic shock, it is not known if $PaCO_2$ manipulation differentially affects long-term neurological outcome. However, from the standpoint of preserving cerebral oxidative metabolism, hypercapnia should be avoided and hypocapnia or normocapnia should be applied during hemorrhagic shock. Considering the possible circulatory and hyperglycemic effects of hypocapnia, normocapnia might be the appropriate ventilatory strategy.

In conclusion, the effect of different $PaCO_2$ manipulations on cerebral oxidative metabolism was studied using a dog model of hemorrhagic hypotension. Hypotension at LLA level produced brain acidosis in spite of the maintenance of CBF and $CMRO_2$. The effects of $PaCO_2$ manipulation on cerebral oxidative metabolism were similar in hypocapnia and normocapnia, being worse with hypercapnia. Normocapnia was considered to be the appropriate ventilatory strategy during hemorrhagic hypotension, as hypocapnia accompanied marked tachycardia and hyperglycemia.

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