Arterial blood gas management in retrograde cerebral perfusion: the importance of carbon dioxide

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Abstract

Objectives: Many interventional physiological assessments for retrograde cerebral perfusion (RCP) have been explored. However, the appropriate arterial gas management of carbon dioxide (CO₂) remains controversial. The aim of this study is to determine whether alpha-stat or pH-stat could be used for effective brain protection under RCP in terms of cortical cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO₂), and distribution of regional cerebral blood flow.

Methods: Fifteen anesthetized dogs (25.1 ± 1.1 kg) on cardiopulmonary bypass (CPB) were cooled to 18°C under alpha-stat management and had RCP for 90 min under: (1), alpha-stat; (2), pH-stat; or (3), deep hypothermic (18°C) antegrade CPB (antegrade). RCP flow was regulated for a sagittal sinus pressure of around 25 mmHg. CBF was monitored by a laser tissue flowmeter. Serial analyses of blood gas were made. The regional cerebral blood flow was measured with colored microspheres before discontinuation of RCP. CBF and CMRO₂ were evaluated as the percentage of the baseline level (%CBF, %CMRO₂).

Results: The oxygen content of arterial inflow and oxygen extraction was not significantly different between the RCP groups. The %CBF and %CMRO₂ were significantly higher for pH-stat RCP than for alpha-stat RCP. The regional cerebral blood flow, measured with colored microspheres, tended to be higher for pH-stat RCP than for alpha-stat RCP, at every site in the brain. Irrespective of CO₂ management, regional differences were not significant among any site in the brain.

Conclusions: CO₂ management is crucial for brain protection under deep hypothermic RCP. This study revealed that pH-stat was considered to be better than alpha-stat in terms of CBF and oxygen metabolism in the brain. The regional blood flow distribution was considered to be unchanged irrespective of CO₂ management. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Retrograde cerebral perfusion; Alpha-stat; pH-stat; Deep hypothermia; Carbon dioxide

1. Introduction

Many physiological interventions have been assessed with the aim of improving patient outcomes from retrograde cerebral perfusion (RCP). The effects of hemodilution, oxygenation, and perfusion flow and pressure have been discussed previously. However, we did not conclude which was the better strategy for proper arterial gas management of carbon dioxide (CO₂) — alpha-stat or pH-stat.

This study was undertaken to confirm the efficacy of arterial blood gas management to improve the cerebral outcome during RCP. The specific aim of this study was to determine if acute manipulations of CO₂ could be effective for brain protection in terms of the cortical cerebral blood flow (CBF), cerebral metabolism for oxygen, and the distribution of regional blood flow under a constant level of perfusion pressure and body temperature.

2. Methods

Fifteen adult mongrel dogs (weighing 25.1 ± 1.1 kg) were used in this study. All received humane care in compliance with the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health (NIH publication No. 85-23, Revised 1985). The dogs were premedicated with ketamine (15 mg/kg i.m.) and sodium pentobarbital (35 mg/kg i.v.). Anesthesia was maintained with an additional dose of sodium pentobarbital (0.5–1.0 mg/kg) as required. The dose of sodium pentobarbital was equivalent between groups.

Under general anesthesia, craniotomy was performed to expose the dura matter and superior sagittal sinus. The probe
of a laser tissue flowmeter (ALF21, Advance Co. Ltd.) was placed onto the cortical surface of the left temporal lobe to monitor the CBF. In addition, we inserted an indwelling needle into the exposed superior sagittal sinus for pressure monitoring.

A median sternotomy was then performed. Heparin (300 U/kg) was administered and an arterial 14-French cannula was inserted into the right femoral artery. Venous drainage to the pump circuit was via a right atrial 32-French cannula. Cardiopulmonary bypass (CPB) was then instituted. The blood was circulated by a roller pump through a combined heat exchanger and oxygenator (Capiox SX (M), Terumo Co. Ltd.). Under RCP, the in-flow line to the brain was kept at 53.0 \(^\circ\)C, and carbon dioxide tension, and pH (ABL 4, Radiometer Co. Ltd.). Under RCP, the in-flow line to the brain was kept at a sagittal sinus pressure of around 25 mmHg (22.5 \pm 0.4 mmHg). During RCP, the proximal arterial cannula was set at a pressure of 35–40 mmHg. The perfusion pressure was at 35–40 mmHg – frequently, the perfusion pressure was at 35–40 mmHg.

2.1.1.1. Cerebral cortical blood flow A laser Doppler flowmeter measured the cerebral cortical blood flow during RCP. CBF was measured at one point during the procedure.

2.1.1.2. Blood gas analysis. Samples from the inflow to, and outflow from the brain were analyzed at 37°C for oxygen and carbon dioxide tension, and pH (ABL 4, Radiometer Co. Ltd.). Under RCP, the inflow to the brain was the maxillary vein and the outflow from the brain was the common carotid artery.

2.1.1.3. Regional cerebral blood flow. The regional cerebral blood flow was measured by colored microspheres. Measurements were made with 15 µm fluorescent polystyrene microspheres (Dye Trak, Triton Technologies, Inc.), using the blood reference sample method. Two million microspheres (15 µm in diameter) were injected over 60 s into the inflow line to the brain. At completion, the brain was removed. Tissue samples from the cerebral hemisphere, midbrain, basal ganglia, pons + medulla, and cerebellum were obtained. Chemical digestion and centrifugation processed each specimen. The fluorescence in tissue and blood was determined by spectrofluorometry.

The regional blood flow was calculated from the formula in Eq. (1):

\[
Q_m = \frac{Am \times Qt/Ar}{Am/Ar}
\]

where:

- \(Q_m\): regional tissue blood flow;
- \(Am\): absorption unit of sample/g;
- \(Qt\): withdrawal rate of reference blood from the in nominate artery (ml/min);
- \(Ar\): absorption unit of the whole blood withdrawn.

2.2. Statistical analysis

Systemic physiological data were initially analyzed using a non-parametric multiple comparison test (Kruskal–Wallis test) and, if significance was proved, an analysis of variance was performed using multivariate comparison (Games–Howell test). Comparisons between two RCP groups were made using the Mann–Whitney U-test. All data are presented as means \pm standard error of the mean. Differences at \(P < 0.05\) were considered to be significant.
difference between RCP-pH and antegrade perfusion (Fig. 1). The %CBF and %CMRO₂ were significantly lower in the alpha group than in the antegrade group (Figs. 1 and 2). RCP flow rate, f-CMRO₂, and CVR under RCP did not differ between the two RCP groups (Table 2).

In comparing the two RCP time-related subgroups, no significant difference was found in oxygen extraction, %CBF, or %CMRO₂ (Figs. 3 and 4). The %CBF and %CMRO₂ tended to be lower in RCP 75,90 than in RCP 45,60. In RCP 75,90, the %CMRO₂ for pH-stat was significantly higher than that for alpha-stat.

Regional cerebral blood flow, measured by the colored microspheres, tended to be higher for pH-stat RCP than for alpha-stat RCP, in every site in the brain. Only in the pons + medulla was the blood flow response to CO₂ significantly different during RCP (Table 3). Irrespective of CO₂ management during RCP, regional differences were not significant among any site in the brain (Table 3; Fig. 5). The CMRO₂ calculated using CBF, as measured by the colored microsphere method, was 0.23 ± 0.07 for alpha-stat RCP and 0.44 ± 0.10 for pH-stat RCP, and 0.33 ± 0.06 in antegrade perfusion under alpha-stat.

4. Comments

There have been many experimental studies on the effects of deep hypothermic circulatory arrest and RCP. However, the principal debate over PaCO₂ has concerned the advantages or disadvantages of alpha-stat or pH-stat management. The aim of this study was to clarify if acute manipulations of CO₂ could be effective for brain protection in terms of the CBF, cerebral metabolism for oxygen, and the distribution of regional blood flow.

In dogs, the main drainage vein from the brain is the maxillary vein, and there are competent venous valves in the proximal portion of the external jugular vein. The internal jugular vein is almost not developed and of almost no importance. There are two cervical branches from the aortic arch; the brachiocephalic artery and the left subclavian artery. Also, bilateral common carotid arteries and the right subclavian artery arise from the brachiocephalic artery. Compared with humans, the internal carotid artery is very small in dogs. Therefore, in this study, the inflow to the brain under RCP was the maxillary vein and the outflow from the brain was the common carotid artery during RCP, and we hypothesized that circulation of the brain could be separated from the head circulation. In the preliminary study, blood gas analysis gave the same results between the internal and the common carotid artery, between the superior sagittal sinus and the maxillary vein.

The perfusion pressure was around 20–25 mmHg in the superior sagittal sinus under RCP, which was described as appropriate in previous reports [1–5]. The retrograde brain perfusion flow rates were a little bit higher in comparison with previous studies because of the anatomical difference between species.

We measured CBF and CMRO₂ under deep hypothermic antegrade perfusion as the control for comparison with those under RCP. Several previous papers have reported the optimal perfusion rate during deep hypothermia [6–8]. Miya-moto et al. considered the optimal perfusion flow rate for the...
brain during deep hypothermic CPB at 20°C to be 30 ml/kg per min, with a possible oxygen debt resulting in anaerobic metabolism if the perfusion flow rate was maintained at 15 ml/kg per min or less [6]. Watanabe reported that antegrade perfusion was safe when the perfusion flow was about 40 ml/kg per min at a pressure of 10–30 mmHg, and that low-flow perfusion at a pressure of 20 mmHg provided cerebral vasorelaxation and aerobic metabolism during operations conducted at 20°C [7]. In the present study, a perfusion flow of around 50 ml/kg per min was necessary to maintain the perfusion pressure at around 35–40 mmHg at 18°C. Tanaka et al. reported in an experimental study of dogs that in the selective cerebral perfusion system at 20°C, the cerebral blood flow remained constant down to a perfusion pressure of 40 mmHg and then steeply declined, and CMRO₂ also kept a constant level down to 30 mmHg and then fell abruptly [8]. Pressure-regulated or flow-regulated optimal perfusion under deep hypothermic CPB, which is preferable, needs to be studied from various viewpoints.

We used a laser tissue flowmeter for measuring the CBF. Chen et al. published the first study on the use of a laser Doppler flowmeter in the brain [9]. A laser Doppler flowmeter was used to assess the level of reduction of local cortical CBF by various techniques of cerebral cortical infarction in the vascular bed of the middle cerebral artery. Since then, the use of laser Doppler flowmeters for monitoring CBF has been expanded, and validation studies in the central nervous system have shown the reliability of this technique [10]. The laser tissue flowmeter is useful for continuous monitoring, but there appears to be no universal calibration factor for the method [11–13]. Thus, we measured the CBF at one point through the procedure from which the percentage of the baseline level was evaluated.

We calculated CMRO₂ as an estimate of oxygen metabolism. Oxygen extracted in the brain is used both to support electrophysiological function and to maintain cellular integrity. CMRO₂ is a gold standard for global metabolism. However, there are some difficulties in measuring brain metabolism, especially during RCP in the dogs. There are some anatomical difference between humans and dogs, and there are veno-venous shunts in the brain. We hypothesized that circulation of the brain could be separated from the head circulation during RCP and we calculated CMRO₂ using the Fick principle. CMRO₂ was dependent on CBF.

Fig. 1. %CBF of the cortex. There was no significant difference between A and B using the Mann–Whitney U-test.

Fig. 2. %CMRO₂ significant difference between A and B using the Mann–Whitney U-test.

Fig. 3. %CBF and RCP time. (Left) RCP 45,60; (right), RCP 75,90 in each subgroup. (Left) Alpha-stat RCP; (right), pH-stat RCP in each subgroup.
and oxygen extraction, neither of which differed significantly between the time-related subgroups during this study. We also calculated f-CMRO2 and it did not differ between alpha- and pH-stat RCP.

In previous reports, CMRO2 of dogs was reported as 0.45–0.47 in antegrade perfusion (pressure-regulated) at 18°C [14,15]. Watanabe et al. reported that under mild hypercarbic flow-regulated antegrade perfusion (40 ml/kg per min) at 20°C, the CMRO2 was 0.47, and this was 0.62 after 60 min [7]. In our study, the CMRO2 calculated using CBF measured by the colored microsphere method was 0.23 ± 0.07 in alpha-stat RCP and 0.44 ± 0.10 in pH-stat RCP, and 0.33 ± 0.06 in antegrade perfusion under alpha-stat. Also, the %CMRO2 was higher for RCP-pH than for RCP-alpha, but showed no significant difference between RCP-pH and antegrade perfusion. Tanaka et al. reported, in an experimental study in dogs, that after core cooling at a constant perfusion flow rate of 80 ml/kg per min under alpha-stat, the CBF was significantly reduced to 10.0 ± 1.1 ml/100 g per min at 20°C (20 ± 2% of that at 37°C) and the %CMRO2 was reduced to 18 ± 2% [8]. If the %CMRO2 in the antegrade perfusion group is supposed to be the standard value for dogs at 18°C and CMRO2 is dependent mainly on body temperature, it is probable that alpha-stat RCP does not supply sufficient blood flow for cerebral oxygen requirements at 18°C, and that the cerebral blood flow under pH-stat RCP is not excessive with respect to cerebral oxygen demand. From our results, CBF under pH-stat RCP was considered not to be excessive for global tissue oxygen demand compared with deep hypothermic antegrade perfusion under alpha-stat.

We evaluated the difference in regional blood flow in the brain under RCP according to CO2 management. Marcus et al. reported that in dogs, 15 μm was an appropriate size sphere to use for measurement of cerebral blood flow because shunting was minimal, the distribution was not artefactually distorted, and the measurements were reproducible [16]. Therefore, we measured regional blood flow in the brain using 15 μm colored microspheres.

There have been several reports on flow distribution in the brain during RCP [5,17–23]. From the standpoint of regional blood flow, there were studies using microspheres [17], Indian Ink [18], the single photon emission computed tomography technique (SPECT) [19–21], magnetic resonance (MR) perfusion imaging [22]. However, the results for flow distribution under RCP were varied, possibly because of differences in species, perfusion pressure, and body temperature. There are no previous reports about the regional flow distribution under RCP in terms of CO2 management. In our study, regional differences in blood flow before the discontinuation of RCP for 90 min were not significant, irrespective of CO2 management.

Some previous reports have concerned the distribution under RCP from the standpoint of regional metabolism using histopathological studies [23] and pH-mapping [5]. The caudate nucleus was reported to be more susceptible...
to ischemic changes than the other areas in the brain under RCP, as revealed by histological examination and pH-mapping. The observed differences in the distribution of regional blood flow and metabolism were considered to be due to inappropriate coupling with regional blood flow and metabolism or to variations in the vulnerability to ischemic change. An evaluation of the relationship between regional flow and metabolism in the brain should be undertaken in a further study.

From our results, pH-stat is considered to be neuroprotective under RCP, in that the cerebral oxygen supply and extraction are enhanced. Under RCP, the pH-stat strategy is considered not to be a luxury, but rather a necessary compensatory management of the leftward shift of the oxyhemoglobin dissociation curve induced by hypothermia, when perfusion flow is limited compared with antegrade perfusion [24]. The reserve for buffering acid is considered to be kept even in pH-stat under deep hypothermia. The difference between the pH of the extracellular environment and that of the neutral point of water appears to be constant for a given species. This relationship is achieved through the interactions of a multi-buffer system which requires not only the unique properties of the protein buffer, imidazole of histidine, and N-terminal alfa-amino groups, but also the precise regulation of the bicarbonate/carbonic acid ratio. By protecting from change the fractional dissociation of the peptide-linked histidine imidazole groups, the protein enzymatic and transport activities dependent on protein charge state, are available to the organism at all body temperatures [25].

From these results, CBF in pH-stat is considered not to be excessive with respect to tissue oxygen demand. The regional blood distribution is unchanged irrespective of CO₂ management.

5. Conclusion

Carbon dioxide management is crucial for brain protection under deep hypothermic RCP. This study revealed that pH-stat was preferable to alpha-stat in terms of CBF and oxygen metabolism in the brain. The regional blood flow distribution was believed to be unchanged, irrespective of CO₂ management.

References

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Appendix A. Abbreviations

- O2 content, oxygen content (vol.%)
- O2 extraction = O2 content (I) – O2 content (O)
- CBF (ml/min per 100 g), cerebral blood flow of the cortex
- CMRO2 (ml/min per 100 g), cerebral metabolic rate for oxygen = (O2 content (I) – O2 content (O)) × CBF × 0.01
- RCP flow rate, perfusion flow rate to the brain during RCP
- f-CMRO2, O2 extraction × RCP flow rate (ml/min per kg)
- CVR under RCP, perfusion pressure (mmHg) during RCP/RCP flow rate
- %CBF = 100 × CBF(DH)/CBF(PRE)
- %CMRO2 = 100 × CMRO2(DH)/CMRO2(PRE)
- (I), data for inflow to the brain; (O), data for outflow from the brain
- (DH), data measured under deep hypothermic RCP or antegrade perfusion
- (PRE), data measured before cardiopulmonary bypass
- (CPB), data measured after the establishment of cardiopulmonary bypass before cooling