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ORIGINAL ARTICLE

Alpha-Stat Versus pH-Stat Guided Ventilation in Patients with Large Ischemic Stroke Treated by Hypothermia

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Abstract
Background Moderate hypothermia (MH) is a therapeutic approach for ischemic stroke as well as cardiac arrest. Two different technical strategies of ventilation during MH called alpha- and pH-stat dramatically influence cerebral blood flow (CBF). In turn this might influence neuronal damage and intracranial pressure (ICP). Therefore, effects of ventilation on CBF and ICP were measured in patients undergoing MH because of large ischemic stroke to address optimal ventilation management.
Methods Eight patients ($n = 8$) with large ischemic stroke in the territory of the middle cerebral artery (MCA) were treated by MH of 33°C within 24 h after symptom onset. MH was applied at least for 72 h. Each day, patients were ventilated repetitively with either alpha-stat or pH-stat for 60 min periods. Alpha-stat was applied between the measurements. ICP, CBF, and mean arterial blood pressure (MABP) were measured. The xenon clearance method was used to assess CBF at the bedside.
Results There were no significant differences between ICP values for alpha-stat or pH-stat during days 1 and 2 after induction of hypothermia. However, ICP was higher in the pH- as compared to the alpha-stat group ($P < 0.05$) and exceeded a mean of 20 mmHg on day 3. pH-stat led to a significant increase of CBF in all measures ($P < 0.05$), while MABP was unaffected.
Conclusions pH-stat implies a better CBF to the injured brain, while it might be dangerous by elevating ICP in more subacute stages.

Keywords Cerebral blood flow · Ischemia · ICP · Brain edema · Stroke

Introduction

Hypothermia has impressive neuroprotective effects in animal models of acute brain injury such as focal and global cerebral ischemia depending on onset of therapy and duration [1, 2]. In general, therapeutic hypothermia can be subdivided to mild hypothermia (34.0–35.9°C), moderate hypothermia (32.0–33.9°C), and deep hypothermia (<32°C) [3]. However, the effectiveness of cooling in the clinical setting is still a matter of discussion. The only confirmed indication today seems to be the treatment of a subgroup of cardiac arrest patients [4], in whom early hypothermic treatment resulted in a favorable clinical outcome and survival. Although the efficacy of moderate hypothermia (MH) in patients with acute ischemic stroke has not yet been evaluated, previous studies documented its safety and feasibility [5, 6].

It can be suggested that several undefined methodological aspects might interfere with the potential neuroprotective properties of MH in ischemic stroke patients [3]. Cerebral blood flow (CBF) is the critical factor in acute ischemic stroke. The extent of CBF decrease determines the ischemic core and surrounding penumbra. While the ischemic core cannot be saved be any intervention, the ischemic penumbra is the major target for

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acute stroke therapy. CBF and function of the cerebral tissue is decreased, but restoration of CBF and probably other interventions may save these penumbral regions [2]. In accordance, thrombolysis by rt-PA has been shown to save ischemic brain tissue and improve neurological function. It is the only successful therapy for acute ischemic stroke as shown for example by the National Institutes of Neurological Disorders and Stroke (NINDS) study, so far [7]. So, interventions that influence CBF in the acute phase of ischemic stroke are suggested to influence the extent of the ischemic lesion and therefore neurological outcome. As hypothermia is a potent neuroprotective method and is clinically feasible, interventions that interfere with CBF during hypothermic treatment must be assessed. As seen in cardiac bypass surgery, there are basically two different ventilation strategies during hypothermia that dramatically influence CBF [8, 9]: during alpha-stat management, arterial CO_2 tension ($Paco_2$) is maintained at 40 mmHg when measured at 37°C. The dissociation fraction of the imidazole moiety of histidine is thereby constant, whereas pH changes parallel to the neutral point of water. In contrast, during pH-stat management, $Paco_2$ is corrected according to the patient's actual body temperature [8, 9]. Because of the increased gas solubility during hypothermia, the alpha-stat strategy results in relative hyperventilation, which alters cerebral blood flow (CBF) [8–10]. Alpha-stat management is considered to be the standard ventilation mode for patients undergoing cardiac bypass surgery in deep hypothermia [9, 10]. In these patients, lower CBF might result in diminished delivery of embolic material to the brain and therefore lead to a better outcome compared to pH-stat ventilation [11].

Although CBF differs essentially during alpha- and pH-stat and CBF is so important in acute brain injury, there are no clinical investigations in global and focal cerebral ischemia concerning this issue. A recent experimental study showed that pH-stat management during early hypothermia reduced cerebral infarct volume in a suture occlusion model of focal cerebral ischemia compared to alpha-stat management [8]. However, there are clinical situations in which increased CBF might be harmful due to increased cerebral blood volume leading to a rise of intracranial pressure (ICP).

Since there is no clinical data at all, we investigated the influence of different ventilation regimens in patients with hypothermia and ischemic stroke. The objectives of the study were (1) whether alpha- or pH-stat regimen significantly alters CBF in this subgroup of stroke patients and if so, (2) whether this influences ICP as a critical factor in patients with large stroke. CBF was assessed using the Xenon clearance technique, which is a bedside measurement technique and results in absolute CBF values [12].

Materials and Methods

Patient Treatment

After approval by the local ethics committee, eight patients were enrolled in this study. They were admitted to the neurological intensive care unit (NICU) within 24 h after symptom onset. All patients suffered from a large ischemic stroke that was confirmed by cranial computer tomography (CT) and involved more than 60% of the territory supplied by the middle cerebral artery (MCA).

All patients were treated with MH (body core temperature of 33°C) according to our institutional protocol. They were sedated with midazolam. Fentanyl was used for analgesia and atracurium for neuromuscular blockade. MH was initiated as soon as possible within 24 h of stroke onset. After reaching the target body core temperature of 33°C, MH was sustained for 72 h. The target rewarming rate was 1°C/8 h, while the maximal rewarming rate did not exceed 0.2°C/h. Patients were positioned in the 30° head-up position and were ventilated with a volume-controlled, pressure-regulated mode, and an inspiratory/expiratory ratio of 1:2 (Servo Ventilator 300, Siemens, Germany). MH initiation and maintenance using endovascular cooling, was described elsewhere [13]. In brief, mean arterial pressure was invasively monitored by means of a catheter inserted in the radial artery. Intracranial pressure was monitored by parenchymal (Codmann, Johnson & Johnson) catheters, inserted ipsilateral to the affected hemisphere. Body temperature was continuously monitored with a Foley temperature catheter with a temperature resolution of 0.1°C, inserted in the bladder (Mona-therm, Mallinckrodt). The lower limit of cerebral perfusion pressure tolerated was 70 mmHg; crystalloid or colloid fluids were used as first choice to increase arterial blood pressure, followed by vasopressors when necessary.

Measurement of CBF

Bedside CBF was measured using the intravenous 133Xe clearance technique [14] with a portable, commercially available apparatus (Cerebrograph Cortexplorer; Ceretronix, Randers, Denmark) as previously described [15]. The CBF15, an index of mean gray and white matter flow, was determined according to Obrist and Wilkinson [16]. About 20 to 30 mCi of Xenon-133 were dissolved in saline and injected into the central venous line of the patient. A Ceretronix Cerebrograph Cortexplorer 16 (Randers, Denmark) measured gamma radiation from Xenon-133 using eight detectors positioned over each cerebral hemisphere. Two detectors are placed on the frontal part of the brain, one on the central region, three on the temporal part of the brain, one on the parietal part, and one on the occipital part.

End-tidal Xenon-133 was measured simultaneously to estimate arterial Xenon-133 concentration. The duration of each CBF measurement was 11 min. Data were collected by a laptop computer, and the mean hemispheric and global CBF_{15} were calculated. CBF_{15} is a CBF parameter proven to be very stable in patients with reduced flow [12, 17, 18], calculated using a two-compartment mathematical model. Pertinent clinical and physiologic data (MABP, ICP, CPP, $Paco_2$, body temperature, and vasoactive drugs) were recorded at the time of study.

Ventilation Management and Study Protocol

In general, patients were ventilated by alpha-stat management when no CBF measurements were performed. For alpha-stat management, arterial blood gases were measured at 37°C and ventilation parameters (tidal volume and frequency) adjusted to result in an arterial carbon dioxide tension of 5.3 kPa and arterial pH of 7.40. In pH-stat management, blood gases were measured at the patient's temperature (i.e. 33°C), and the ventilation parameters adjusted to maintain P_{aCO2} at 5.3 kPa and pH 7.40.

CBF measurements were performed at 24–28 h, 48–52 h, and 72–76 h after stroke onset (Fig. 1). The ventilation management for the first measurement was chosen randomly starting either with alpha-stat management or pH-stat management followed alternatively by the alternative modus. For randomization, an envelope was drawn in which the first ventilation management was indicated. Before each CBF measurement, arterial blood gases had to be stable on the desired level for at least 45 min. Therefore, every 5–10 min arterial blood gases were taken to assure stable ventilation in the desired mode. After ventilation by alpha-stat or pH-stat for a total of 60 min, the CBF measurement was performed. After the first measurement, the patient was again ventilated by alpha-stat or pH-stat for a total of 60 min followed by the second Xenon injection. The same procedure was done for the third CBF-calculation.

Statistical Analysis

Statistical analysis was performed with StatView statistical software. Data were expressed as mean ± SD and compared with multiple *t* test and analysis of variance (ANOVA) with Bonferroni correction. A $P < 0.05$ was considered statistically significant.

Results

Patient Data

Eight patients (5 men, 3 women) with a mean age of 67.7 ± 5.5 years were examined. MH was initiated 15.8 ± 2.7 h (range 10–18 h) after stroke onset. The initial temperature of the eight patients was 37.4 ± 0.5°C (range 36.4–38°C). Target temperature was reached 3.1 ± 0.5 h (range 2.5–3.5 h) after initiation of cooling. Duration of MH was 117.6 ± 3.9 h (range 115–123 h).

Physiological Variables

Physiological variables are shown in Table 1. As intended, $PaCO_2$ differed significantly between the groups when recalculated for the same temperature.

Intracranial Pressure

No significant differences in ICP were observed between the two ventilation groups on day 1 (9.1 ± 2.4 vs. 10.4 ± 2.6 mmHg, alpha- and pH-stat, respectively). Similar values were measured during day 2 (11 ± 0.8 vs. 12.8 ± 0.9 mmHg, alpha- and pH-stat, respectively). On

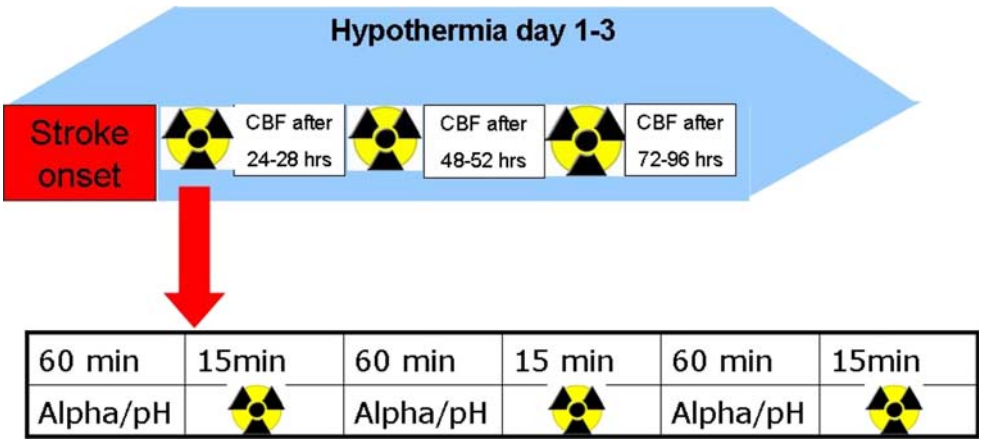

Fig. 1 Schematic study set up. CBF was done between the following periods after stroke onset during hypothermia: 24–28 h, 48–52 h, and 72–76 h. Alternate ventilation by alpha- or pH-stat was done for 60 min followed by Xenon measurement

Table 1 Physiological variables

	Day 1		Day 2		Day 3	
	ph-stat	Alpha-stat	ph-stat	Alpha-stat	ph-stat	Alpha-stat
Bladder temperature	33 ± 0.1	33 ± 0.1	33 ± 0.2	33 ± 0.2	33 ± 0.1	33 ± 0.1
BGA uncorrected						
pH	7.31 ± 0.02	7.35 ± 0.05	7.32 ± 0.04	7.36 ± 0.06	7.31 ± 0.04	7.35 ± 0.02
P_{aCO2} (mmHg)	47 ± 4*	40 ± 3	48 ± 4*	41 ± 3	49 ± 2*	39 ± 4
P_{aO2} (mmHg)	110 ± 23	123 ± 15	106 ± 19	117 ± 23	109 ± 31	119 ± 21
Base excess (mmol/l)	5 ± 3.4	3.5 ± 3	4.5 ± 3	1 ± 5.1	0.2 ± 4	1.2 ± 5
Plasma glucose (mg/dl)	90 ± 15	93 ± 18	90 ± 15	90 ± 15	90 ± 15	90 ± 15
MABP (mmHg)	101 ± 23	105 ± 29	98 ± 32	103 ± 35	87 ± 25	89 ± 18
Heart rate (beats/min)	68 ± 12	72 ± 13	78 ± 11	82 ± 23	73 ± 22	79 ± 24

Values for blood gas analysis are shown uncorrected for the patients' temperature to compare alpha-stat und pH-stat groups. The values were recorded directly before the Xenon investigation. The ANOVA test was used for statistical analysis. The asterisks indicate significant differences (P value of <0.05)

BGA = blood gas analysis; P_{aCO2} = arterial carbon dioxide tension; P_{aO2} = arterial oxygen tension; MABP = mean arterial blood pressure

day 3, ICP increased in both groups, but was significantly higher during pH-stat management as compared to alpha-stat (21.1 ± 2.1 vs. 15.2 ± 2.1 mmHg, respectively, $P < 0.01$, ANOVA). On day 3, two patients developed minor pupil dilatation on the side of infarction during pH-stat ventilation which disappeared during alpha-stat ventilation. As alpha-stat ventilation was the standard ventilation regimen for all patients outside the Xenon-measurements, no further efforts were done to counteract the increased ICP during pH-stat. In all patients, increased values disappeared when switching back to alpha-stat.

Cerebral Blood Flow

Mean global CBF (gCBF) was higher under pH-stat as compared to alpha-stat ventilation throughout the three examination days (all $P < 0.05$, ANOVA).

At day 1, the mean gCBF was 66.75 ± 12.2 ml/100 g*min in the pH-stat compared to 33.3 ± 5.1 ml/100 g*min ($P < 0.05$). On day 2, the mean gCBF was 58.1 ± 13.3 ml/100 g*min in the pH-stat compared to 36.5 ± 5.9 ml/100 g*min ($P < 0.05$). Similar results were shown on day 3. GCBF was 62.4 ± 11.5 ml/100 g*min in the pH-stat compared to 34.3 ± 7.9 ml/100 g*min ($P < 0.05$).

Similar results were calculated when analyzing regional CBF (rCBF) in each hemisphere. rCBF was higher at each measurement during pH-stat compared to alpha-stat ($P < 0.05$). Figure 2 shows the rCBF of the ischemic and non-ischemic hemisphere. Table 2 shows the regional CBF in the 16 different brain regions during alpha- and pH-stat ventilation. As indicated, most of the CBF values were larger during pH-stat management in the ischemic and non-ischemic hemisphere compared to the corresponding side during alpha-stat management ($P < 0.05$).

Discussion

We sought to define the optimal ventilation strategy for patients treated with MH after acute ischemic stroke. To our knowledge, this topic has not been studied in stroke patients or even patients after cardiac arrest. The main observation of this study was that pH-stat management led to higher CBF compared to alpha-stat at each time point assessed during the first 3 days of MH. ICP on the other hand was not changed by ventilation strategies on days 1 and 2, but significantly higher under pH-stat ventilation on day 3. As CBF is a major determinant in acute cerebral ischemic disease such as ischemic stroke, these data suggest high relevancy when treating patients by hypothermia in the future.

Stroke and Hypothermia

So far, hypothermia is the only successful neuroprotective method as it improved patients' outcome after cardiac arrest. While animal data indicate neuroprotective effects for other acute brain injuries such as stroke [1, 2], results of clinical trials in stroke remain disappointing until now. It can be suggested that many unaddressed, but important factors could have led to these disappointing results [3]. We suppose by the data of the recent manuscript and previous animal data [8], that CBF influenced by different ventilation strategies might be a major unaddressed factor for stroke treatment. So far, there are basically two

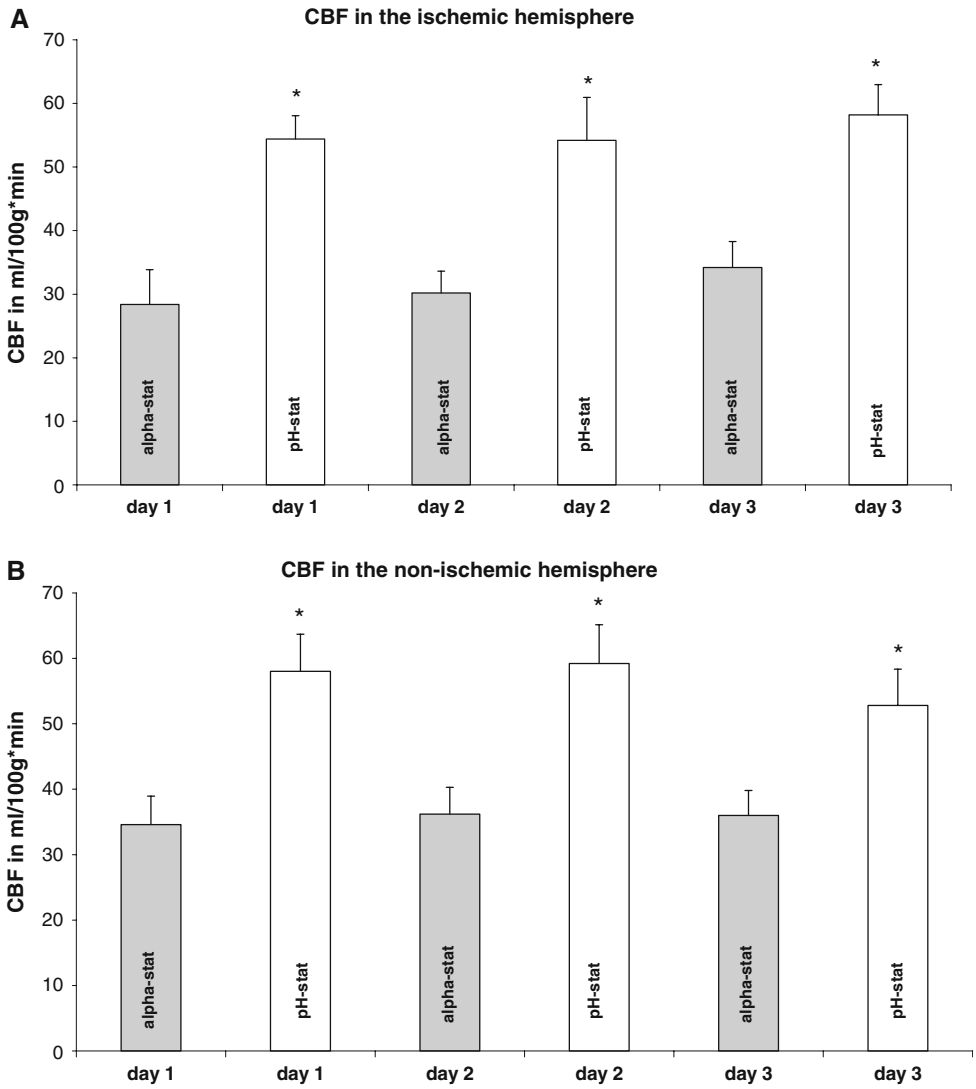

Fig. 2 Cerebral blood flow analyses for the ischemic hemisphere (**a**), and the non-ischemic hemisphere (**b**). CBF was larger at each time point for pH-stat ventilation compared to alpha-stat. The asterisks indicate significant differences (P value of <0.05)

hypothermic treatment strategies in acute stroke: neuroprotection and ICP-control.

Rapid induction of hypothermia in the neuroprotective time window has not been investigated sufficiently [3] as the time to goal temperature in awake stroke patients was between 3 and 9 h from symptom onset. The second approach was the use of moderate hypothermia in sedated and ventilated patients with severe stroke. Most of these patients had a large infarction in the territory supplied by the MCA and required ventilation due to decreased level of consciousness caused by brain swelling and secondary rise of ICP [5]. For these patients, clinical therapy is so far limited to conservative treatment of the elevated ICP, e.g. by osmotherapeutics or experimental treatment strategies like hemicraniotomy or moderate hypothermia [13, 19]. While there is no large randomized trial investigating the effects of moderate hypothermia on outcome, there is a good sign for effectivity in centers that enrolled relatively larger number of patients [5]. Controlling ICP by hypothermia was the major treatment goal and has been shown to be feasible. For both, neuroprotective effects and ICP-control, ventilation management was not investigated so far, but can be considered to have major influence on the fate of brain tissue after stroke onset.

Experimental Data on Ventilation During Stroke and Hypothermia

In hypothermia, there are to date only animal data investigating the effects of different ventilation strategies during therapeutic hypothermia in focal cerebral ischemia [8, 20]. While Nagai showed no differences in infarct size [15], Kollmar et al. demonstrated a significant effect [20]. In the very early reperfusion period (5 h after transient focal cerebral ischemia), pH-stat management significantly decreases cerebral infarct volume and edema as compared to alpha-stat during moderate hypothermia, probably by increasing CBF [8]. Because these results were observed

Table 2 Regional CBF

Hemisphere Brain region	Non-ischemic Alpha	Ischemic Alpha	Non-ischemic pH	Ischemic pH
*Regional CBF in mg/100 g*min on day 1*				
Frontal superior	31 ± 7	37 ± 16	50 ± 13*	51 ± 15§
Frontal inferior	34 ± 10	37 ± 13	50 ± 14*	46 ± 15§
Central region	33 ± 10	33 ± 11	50 ± 15*	53 ± 14§
Temporal frontal	32 ± 7	39 ± 16	60 ± 14*	57 ± 13§
Temporal medial	31 ± 9	34 ± 12	58 ± 5*	54 ± 11§
Temporal posterior	33 ± 9	39 ± 15	59 ± 15*	61 ± 15§
Parietal	30 ± 9	34 ± 14	54 ± 15*	52 ± 15§
Occipital	32 ± 9	33 ± 14	48 ± 15*	53 ± 16§
*Regional CBF in mg/100 g*min on day 2*				
Frontal superior	32 ± 4	29 ± 5	46 ± 10*	39 ± 8§
Frontal inferior	34 ± 3	30 ± 5	42 ± 11*	49 ± 8§
Central region	35 ± 10	30 ± 9	40 ± 8	39 ± 10§
Temporal frontal	39 ± 9	33 ± 6	50 ± 17*	43 ± 14§
Temporal medial	36 ± 11	34 ± 11	44 ± 10	45 ± 10§
Temporal posterior	46 ± 11	40 ± 10	53 ± 16*	50 ± 10§
Parietal	32 ± 9	33 ± 9	53 ± 13*	43 ± 14§
Occipital	38 ± 12	35 ± 11	46 ± 10	52 ± 9§
*Regional CBF in mg/100 g*min on day 3*				
Frontal superior	32 ± 5	32 ± 5	41 ± 5*	37 ± 5§
Frontal inferior	36 ± 4	27 ± 4	40 ± 7*	37 ± 8§
Central region	39 ± 11	31 ± 10	50 ± 8*	38 ± 9§
Temporal frontal	33 ± 5	43 ± 13	48 ± 9*	46 ± 9
Temporal medial	32 ± 7	36 ± 7	56 ± 12*	54 ± 12§
Temporal posterior	36 ± 5	37 ± 14	50 ± 15*	49 ± 11§
Parietal	35 ± 9	36 ± 10	50 ± 15*	49 ± 11§
Occipital	40 ± 4	34 ± 9	51 ± 11*	46 ± 12§

Regional cerebral blood flow is given in absolute values for each brain regions assessed by the Cortexexplorer. ANOVA was used for statistical analysis to compare CBF on the ischemic side of the brain during alpha-stat versus pH-stat. The same procedure was done for the non-ischemic side. A P value of <0.05 was considered statistically significant indicated by asterisks for the non-ischemic side, a string sign for the ischemic side

only in the early time period after stroke onset, no conclusions can be drawn whether these effects are permanent or transient. Moreover, effects of ventilation strategies on infarct size, CBF, and ICP were not investigated in the clinical or experimental setup during subacute stages of cerebral ischemia and hypothermia.

CBF, ICP, and Techniques of the Recent Study

In the present study, the intravenous Xenon-133 clearance technique [12] was used for measuring CBF. In contrast to Xenon-CT or MRI, it allows the calculation of exact CBF values in repeated measurements without transporting the patient [12, 18, 21]. This is essential, because the transport of patients with space occupying infarcts may be life threatening and alterations of positioning and ventilation make reproducible CBF measurements difficult. In the present study, repeated measurements of CBF and ICP after a defined period of unaltered ventilation lead to reproducible results that were consistent throughout the study. Similar to the experimental study of Kollmar et al. [8], pH-stat results in higher CBF compared to alpha-stat. pH-stat was feasible and safe on days 1 and 2 after stroke onset, since ICP did not reach critical values. However, our data indicate that the benefit of pH-stat management seems to be limited to the first 48 h after stroke onset in the subgroup of patients investigated. After 2 days, pH-stat led to a critical increase of ICP. It can be argued that the increased CBF leads to this effect. The intracranial space of an adult is 1,500–1,700 ml and consists of three major components: brain tissue, cerebrospinal fluid (CSF), and blood. While the brain tissue is visco-elastic and accounts for 85% of the intracranial space, 15% are filled by CSF (5–15% depending on age and stage of cerebral atrophy) and blood. Depending on the grade of vasoconstriction or vasoparalysis, cerebral blood volume (CBV) varies from 3% up to 11% of the intracranial space. It can be argued that an increase of CBV during days 1 and 2 after stroke onset can be compensated by the brain tissue and CSF. However, the natural course of space occupying infarcts leads to an increase of the peri-ischemic edema and therefore the volume of brain tissue may rise to a threshold where small changes in the volume of CSF and blood dramatically raise ICP. Since pH-stat increases CBF by vasodilation, the critical increase of ICP on day 3 is probably caused by an increase of CBV which cannot be compensated. Therefore, other techniques such as cerebral microdialysis might be useful to indicate the turning point when pH-stat should be switched to alpha-stat.

Is an Improved CBF Beneficial after Stroke?

According to experimental data [8], an improved CBF after stroke onset during hypothermia may be beneficial because of a better blood supply to the penumbra. However, it can be speculated that the subgroup of patients with large space occupying infarcts does not have a relevant penumbral zone at all, since hypothermia was initiated 15.8 ± 2.7 h after stroke onset. Still, there is data from clinical MRI-trials that penumbral regions are found even many hours after stroke

onset [22]. Recent data from experimental cardiopulmonary bypass show that pH-stat leads to substantially higher oxygen levels in the brain compared to alpha-stat [23].

It can only be speculated that an improved CBF by pH-stat might result in a more homogeneous temperature profile throughout the brain counteracting a considerable temperature gradient in different brain regions. Therefore, toxic mediators like glutamate or lactate might be eliminated more effectively by a higher CBF.

Limitations

Certainly, the number of patients included into this study is rather small. However, data are so consistent that more patients might not have lead to different results. It can be argued that patients treated within in first hours after stroke onset represent a more relevant patient cohort for these investigations. However, we provide at least a proof of principle that has negotiated so far for acute ischemic brain injury and brain trauma.

Conclusions

Our results show for the first time in stroke patients treated by hypothermia that ventilation strategies have an influence on CBF and ICP. It can be speculated that increased CBF has to some extent beneficial effects during the early stroke period, since increased CBF might rescue critically ischemic tissue. However, a major risk in pH-stat guided ventilation is the critical increase of ICP which could lead to additional brain injury if not noticed and treated. Therefore, ICP measurement is essential in patients that suffer from space occupying lesions.

This study underscores the importance of ventilation management in therapeutic hypothermia. In addition, other methodical aspects such as depth and duration of hypothermia, require more attention in order to transfer the promising results of neuroprotection studies from animals to brain injured patients.

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