

Acid–base management – is it relevant for the study design of hypothermic neuroprotection?

Among the most important controversies in evidence-based medical science is the use of therapeutic hypothermia. Our knowledge about hypothermic brain protection is still limited and several crucial factors such as target brain temperature, start and duration of hypothermia treatment as well as various unknown others still remain to be explored. Recently, the use of therapeutic hypothermia from 32–34°C after cardiac arrest improved neurological outcome in an impressive way [1–3]. This was in contradiction to a large hypothermia trial (NABIS:H), funded by the National Institute of Health (NIH), [4] concerning brain injured patients – subjected to cooling – who failed to demonstrate any improved survival. Soon after publication of the latter study, some methodological aspects were criticised [5–7]. To improve the future accuracy of hypothermia studies, scientists are now being challenged to consider further factors which impact upon brain integrity during ischaemia and trauma [8,9]. Without doubt, among these are considerable changes in the relationship between cerebral blood flow (CBF) and metabolism.

Soon after therapeutic hypothermia was used to slow down metabolic rate of ischaemic tissue – and thereby to reduce the structural damage to tissues – it became obvious that ‘pH management’ has an impact on outcome. Lung ventilation to normocapnia is temperature-dependent since the solubility of gases in blood is increased as temperature is lowered; the pH of arterial blood shifts in parallel to the neutral point of water towards alkalosis. If ‘pH-stat’ management is used during hypothermia, the analytical results of the blood-gas analysis are corrected for the actual lower body temperature thus resulting in a more hypocapnic status. The compensatory reduction of lung ventilation increases the partial pressure of carbon dioxide and thereby augments CBF.

This relative hypoventilation is in contrast to ‘ α -stat’ management where the arterial blood is not corrected for the actual body temperature. α -stat management (so-called *alpha*-stat by the constant alpha dissociation fraction of the imidazole moiety of histidine which is assumed to be responsible for a preserved enzyme and protein activity during hypothermia) mimics the unchanged ventilation of ectothermic vertebrates who do not control pH and temperature.

After the publication of investigations demonstrating a reduced incidence of cerebral emboli following α -stat management during cardiac surgery [10,11], it is generally accepted that lung ventilation of adults during cardiopulmonary hypothermia should be adjusted using α -stat management [12]. Since microemboli during cardiac surgery are primarily associated with the cannulation of large vessels to permit extracorporeal circulation, the role of pH management in neurology and neurosurgery remains unclear. For hypothermic brain protection in these disciplines, until now, α -stat management was preferred due to reports of better preservation of the coupling between CBF and metabolism in animals [13] and patients [14,15]. All cited studies measured either global metabolism (by brain arterial-venous oxygen content difference [13]) or the CBF for either the entire brain or a brain hemisphere by ^{133}Xe clearance of cerebral venous blood and argon wash-in technique, respectively. Independent variations and uncoupling of the global CBF from the global brain metabolism were demonstrated in cardiac surgical patients. Since no clinical study measured regional CBF, the decreased metabolism – together with increased global blood flow during pH-stat management – might have been misinterpreted as flow/metabolism mismatch. Therefore, the impact of the acid-base management on regional CBF and brain metabolism needs to be reconsidered.

Recently, the dose-dependent effect of hypothermia in the range 32–37.5°C on CBF and metabolism (by the local cerebral glucose utilization (LCGU)) was investigated at a local level in non-ischaemic rat brains. It became evident that local CBF/metabolism coupling is well preserved during hypothermia down

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Table 1. Physiological variables of the experimental groups (with permission from [16,17]).

	Normothermic anaesthesia (1 MAC isoflurane)	Mild hypothermia 35°C pH-stat	Mild hypothermia 35°C α -stat	Moderate hypothermia 32°C pH-stat	Moderate hypothermia 32°C α -stat
Pericranial temperature (°C)	37.1 ± 0.2	34.9 ± 0.3*	35.0 ± 0.1*	31.9 ± 0.2*	31.7 ± 0.2*
Arterial pH	7.40 ± 0.03	7.31 ± 0.04	7.35 ± 0.04	7.34 ± 0.03	7.33 ± 0.04
PaO ₂ (kPa)	15.2 ± 3.7	25.2 ± 3.3*	25.3 ± 3.9*	26.4 ± 7.5*	32.9 ± 6.4*
PaCO ₂ (kPa)	5.5 ± 0.5	5.3 ± 0.5	5.5 ± 0.4	5.6 ± 0.9	5.5 ± 0.5
Blood glucose (mmol dL ⁻¹)	10.8 ± 1.6	10.3 ± 2.4	11.1 ± 1.6	13.5 ± 3.1	12.9 ± 2.05
Haematocrit (%)	43 ± 4	44 ± 3	43 ± 6	46 ± 4	44 ± 5
MAP (mmHg)	123 ± 12	104 ± 9 [†]	125 ± 14	134 ± 18	144 ± 17 [‡]
Heart rate (beats min ⁻¹)	353 ± 44	351 ± 36	387 ± 34	367 ± 37	392 ± 27

MAC, minimal alveolar concentration; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; MAP, mean arterial pressure. Each group: $n = 10$, mean ± SD. * $P < 0.05$ vs. normothermic controls, [†] $P \leq 0.05$ vs. α -stat at 32°C, [‡] $P < 0.05$ vs. pH-stat at 35°C.

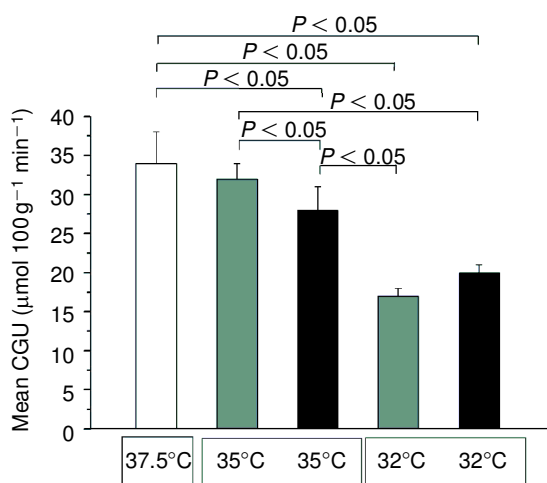


Figure 1.

Effects of the pH management during graded hypothermia on cerebral glucose utilization (CGU) if either α -stat (■) or pH-stat (■) management is used (with permission from [16,17]).

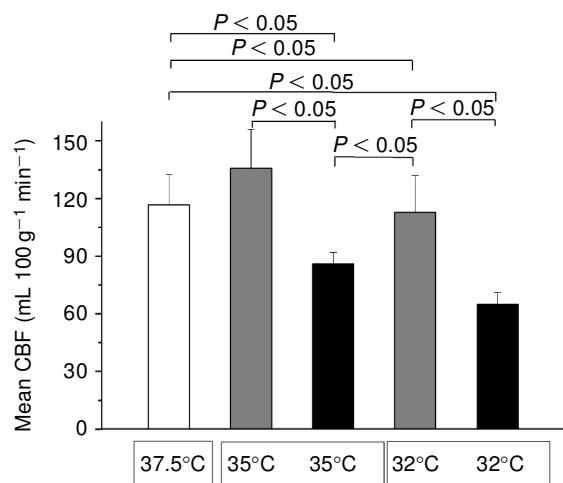


Figure 2.

Effects of the pH management during graded hypothermia on cerebral blood flow (CBF) if either α -stat (■) or pH-stat (■) management is used (with permission from [16,17]).

to at least 32°C – managed by pH-stat [16] – as well as its management by α -stat [17]. To emphasize the effect of acid-base management on CBF and brain metabolism under physiological conditions, pH-stat and α -stat data of the two latter studies were combined and compared. With the exception of an increased oxygen tension in comparison to normothermic animals, physiological variables were comparable between the groups (Table 1).

Cerebral glucose utilization (or brain metabolism)

Compared to normothermic anaesthetized controls, mean cerebral glucose utilization during mild hypothermia (35°C) remained unchanged during

pH-stat management but was reduced during α -stat management by 18% (Fig. 1). During pH-stat and 35°C, local cerebral glucose utilization was decreased only in two regions, but in 20 regions during α -stat (Table 2). During moderate hypothermia (32°C), both pH management reduced mean cerebral glucose utilization (α -stat by 41% and pH-stat by 50%). Local cerebral glucose utilization was reduced during pH-stat in 35 instances and during α -stat in 32 instances out of 41 brain structures. Differences between the pH management on each temperature step were a lower local cerebral glucose utilization in 13 brain structures during mild hypothermia, and an increased local cerebral glucose utilization in two brain structures (cerebellar white and in the reticular part of the substantia nigra) during mild hypothermia by α -stat treatment.

Table 2. Local cerebral glucose utilization of the experimental groups (with permission from [16,17]).

Local cerebral glucose utilization ($\mu\text{mol } 100\text{g}^{-1}\text{min}^{-1}$)	Normothermic anaesthesia 37.5°C	Mild hypothermia 35°C pH-stat	Mild hypothermia 35°C α -stat	Moderate hypothermia 32°C pH-stat	Moderate hypothermia 32°C α -stat
Cerebellum					
Cerebellar cortex	26 \pm 4	25 \pm 2	22 \pm 4	16 \pm 3*	18 \pm 5*
Dentate nuclei	73 \pm 28	84 \pm 21	80 \pm 15	65 \pm 28	90 \pm 20
Medulla-pons					
Vestibular nucleus	77 \pm 26	117 \pm 26	130 \pm 31*	82 \pm 18	112 \pm 26
Cochlear nucleus	82 \pm 19	106 \pm 30	124 \pm 30*	74 \pm 16	98 \pm 11
Superior olive	86 \pm 27	108 \pm 20	110 \pm 23	74 \pm 4	91 \pm 12
Pontine grey	26 \pm 3	27 \pm 2	21 \pm 2*	15 \pm 1*	15 \pm 2*
Lateral lemniscus	56 \pm 5	57 \pm 7	58 \pm 9	34 \pm 10*	45 \pm 7
Mesencephalon					
Inferior colliculus	83 \pm 15	75 \pm 9	75 \pm 7	52 \pm 2*	54 \pm 11*
Superior colliculus	35 \pm 2	30 \pm 1	27 \pm 4*	20 \pm 3*	20 \pm 8*
Substantia nigra c.p.	48 \pm 3	47 \pm 11	58 \pm 11	29 \pm 5*	33 \pm 8*
Substantia nigra r.p.	33 \pm 17	30 \pm 9	46 \pm 8*	18 \pm 7*	30 \pm 7
Diencephalon					
Medial geniculate body	34 \pm 4	28 \pm 2*	22 \pm 2*	19 \pm 3*	16 \pm 3*
Lateral geniculate body	30 \pm 2	29 \pm 4	24 \pm 4*	18 \pm 2*	17 \pm 2*
Mammillary body	55 \pm 6	52 \pm 11	46 \pm 4	35 \pm 5*	37 \pm 5*
Hypothalamus	24 \pm 3	23 \pm 2	15 \pm 3*	12 \pm 1*	12 \pm 3*
Ventral thalamus	28 \pm 5	27 \pm 4	26 \pm 4	15 \pm 2*	18 \pm 1*
Lateral thalamus	40 \pm 6	36 \pm 2	30 \pm 4*	18 \pm 3*	20 \pm 3*
Telencephalon					
Hippocampus CA1	39 \pm 4	34 \pm 5	32 \pm 4	19 \pm 5*	24 \pm 6*
Hippocampus CA2	31 \pm 6	26 \pm 2	23 \pm 2*	15 \pm 1*	13 \pm 3*
Hippocampus CA3	48 \pm 5	50 \pm 10	36 \pm 16	25 \pm 4*	28 \pm 7*
Hippocampus CA4	56 \pm 5	41 \pm 3	41 \pm 7*	25 \pm 4*	24 \pm 2*
Dentate gyrus	35 \pm 6	30 \pm 5	24 \pm 3*	16 \pm 3*	14 \pm 4*
Amygdaloid complex	29 \pm 6	25 \pm 2	17 \pm 3*	9 \pm 2*	12 \pm 2*
Globus pallidus	24 \pm 4	24 \pm 2	19 \pm 3	9 \pm 2*	12 \pm 4*
Caudate nucleus	46 \pm 7	40 \pm 2*	30 \pm 2*	21 \pm 2*	20 \pm 2*
Nucleus accumbens	45 \pm 6	38 \pm 4	32 \pm 6*	20 \pm 5*	18 \pm 4*
Visual cortex	44 \pm 7	42 \pm 3	34 \pm 9	26 \pm 5*	24 \pm 6*
Auditory cortex	49 \pm 4	46 \pm 5	42 \pm 6	32 \pm 4*	29 \pm 7*
Parietal cortex	41 \pm 5	48 \pm 4*	37 \pm 5	27 \pm 2*	26 \pm 4*
Sensory motor cortex	34 \pm 4	36 \pm 3	32 \pm 5	21 \pm 3*	26 \pm 4*
Frontal cortex	35 \pm 5	38 \pm 4	35 \pm 6	21 \pm 3*	25 \pm 5*
Cingulate cortex	43 \pm 7	44 \pm 4	32 \pm 6*	23 \pm 3*	24 \pm 5*
Pyriform cortex	40 \pm 6	45 \pm 3	38 \pm 6	25 \pm 6*	30 \pm 7*
Lateral septal nuclei	24 \pm 4	23 \pm 3	18 \pm 1*	9 \pm 2*	12 \pm 3*
Myelinated fibre tracts					
Internal capsule	12 \pm 4	13 \pm 1	8 \pm 2*	3 \pm 2*	5 \pm 2*
Medial habenulae	58 \pm 7	70 \pm 19	78 \pm 29	48 \pm 9	58 \pm 6
Lateral habenulae	55 \pm 5	50 \pm 12	53 \pm 10	35 \pm 6*	54 \pm 6
Corpus callosum	17 \pm 4	19 \pm 3	11 \pm 4*	6 \pm 4*	8 \pm 2*
Genu of corp. callosum	13 \pm 3	15 \pm 4	8 \pm 2*	3 \pm 2*	4 \pm 3*
Cerebellar white matter	14 \pm 4	15 \pm 2	9 \pm 1*	5 \pm 2*	9 \pm 2*

c.p.: compact part; r.p.: reticular part; corp.: corpus; each group: $n = 10$, mean \pm SD. * $P < 0.05$ vs. normothermic controls. For differences between pH management, see text.

Cerebral blood flow

The mean CBF of anaesthetized controls was unchanged during pH-stat management but was decreased in the α -stat group by 27% during mild hypothermia (35°C) and by 44% during moderate hypothermia (Fig. 2). Local cerebral blood flow was measured in 41 different brain structures (Table 3). Compared to normothermic anaesthesia,

local cerebral blood flow during mild hypothermia (35°C) increased in 13 brain structures with pH-stat management but decreased in 22 structures with α -stat management. During moderate hypothermia (32°C), local CBF decreased in one and increased in two brain structures with pH-stat, but decreased in 31 structures with α -stat (Table 2). Local CBF differences between the pH management strategies were

Table 3. Local cerebral blood flow of the experimental groups (with permission from [16,17]).

Cerebral blood flow (mL 100g ⁻¹ min ⁻¹)	Normothermic anaesthesia 37.5°C	Mild hypothermia 35°C pH-stat	Mild hypothermia 35°C α -stat	Moderate hypothermia 32°C pH-stat	Moderate hypothermia 32°C α -stat
Cerebellum					
Cerebellar cortex	129 ± 30	169 ± 29*	94 ± 12	132 ± 29	72 ± 15*
Dentate nuclei	235 ± 56	396 ± 87*	206 ± 25	268 ± 56	203 ± 45
Medulla-pons					
Vestibular nucleus	237 ± 45	423 ± 63*	312 ± 71	370 ± 81*	259 ± 37
Cochlear nucleus	272 ± 78	338 ± 109	309 ± 74	314 ± 64	210 ± 18
Superior olive	280 ± 52	453 ± 73*	285 ± 67	335 ± 94	237 ± 47
Pontine grey	133 ± 33	180 ± 32*	100 ± 13	155 ± 16	79 ± 10*
Lateral lemniscus	185 ± 52	302 ± 43*	182 ± 20	216 ± 9	138 ± 15
Mesencephalon					
Inferior colliculus	253 ± 43	330 ± 38*	180 ± 24*	251 ± 29	129 ± 15*
Superior colliculus	145 ± 23	177 ± 25	98 ± 13*	167 ± 37	78 ± 13*
Substantia nigra c.p.	145 ± 15	168 ± 48	83 ± 6*	159 ± 38	52 ± 31*
Substantia nigra r.p.	138 ± 17	153 ± 36	82 ± 5*	121 ± 15	52 ± 31*
Diencephalon					
Medial geniculate body	156 ± 27	194 ± 41	101 ± 10	156 ± 58	76 ± 11*
Lateral geniculate body	129 ± 27	159 ± 22*	91 ± 12	153 ± 33	70 ± 6*
Mammillary body	152 ± 23	213 ± 29*	145 ± 20	183 ± 32	119 ± 17
Hypothalamus	96 ± 4	105 ± 11	63 ± 6*	110 ± 19	55 ± 5*
Ventral thalamus	129 ± 25	155 ± 44	65 ± 7*	130 ± 26	62 ± 10*
Lateral thalamus	144 ± 15	144 ± 30	82 ± 10*	153 ± 58	65 ± 8*
Telencephalon					
Hippocampus CA1	115 ± 15	107 ± 18	74 ± 7*	116 ± 44	52 ± 7*
Hippocampus CA2	118 ± 30	116 ± 20	70 ± 10*	112 ± 39	52 ± 6*
Hippocampus CA3	122 ± 21	144 ± 25	83 ± 9*	127 ± 39	60 ± 7*
Hippocampus CA4	135 ± 30	127 ± 17	79 ± 3*	124 ± 48	57 ± 6*
Dentate gyrus	110 ± 24	114 ± 15	65 ± 10*	111 ± 36	48 ± 6*
Amygdaloid complex	92 ± 5	104 ± 20	66 ± 7*	106 ± 28	49 ± 6*
Globus pallidus	86 ± 14	93 ± 22	48 ± 4*	80 ± 40	35 ± 3*
Caudate nucleus	134 ± 11	154 ± 26	91 ± 9*	138 ± 50	66 ± 6*
Nucleus accumbens	137 ± 11	142 ± 26	79 ± 13*	143 ± 52	69 ± 7*
Visual cortex	127 ± 29	153 ± 31	86 ± 6	136 ± 42	74 ± 12*
Auditory cortex	134 ± 25	158 ± 34	112 ± 14	137 ± 42	81 ± 17*
Parietal cortex	127 ± 10	142 ± 40	103 ± 7	118 ± 46	70 ± 10*
Sensory motor cortex	130 ± 25	145 ± 39	95 ± 13	138 ± 44	74 ± 13*
Frontal cortex	124 ± 16	140 ± 13	88 ± 10	128 ± 41	68 ± 10*
Cingulate cortex	147 ± 22	173 ± 41	111 ± 8	145 ± 34	81 ± 5*
Pyriform cortex	109 ± 16	165 ± 26*	121 ± 13	143 ± 39	86 ± 4
Lateral septal nuclei	104 ± 13	122 ± 18	65 ± 11*	105 ± 35	52 ± 5*
Myelinated fibre tracts					
Internal capsule	65 ± 13	68 ± 9	33 ± 3*	48 ± 21	33 ± 5*
Medial habenulae	174 ± 24	219 ± 35*	163 ± 16	189 ± 32	146 ± 19
Lateral habenulae	185 ± 33	258 ± 54	166 ± 17*	201 ± 43*	154 ± 10*
Corpus callosum	62 ± 17	50 ± 2	31 ± 5*	42 ± 7	28 ± 3*
Genu of corp. callosum	65 ± 9	68 ± 9*	36 ± 4*	55 ± 19	28 ± 3*
Cerebellar white matter	73 ± 15	97 ± 11	50 ± 8	69 ± 6	48 ± 13

c.p.: compact part; r.p.: reticular part; corp.: corpus. Each group: $n = 10$, mean \pm SD. * $P < 0.05$ vs. normothermic controls. For differences between pH management, see text.

found during mild hypothermia in all structures except for three (cochlear nuclei, hippocampus CA1, and parietal cortex). Compared to pH-stat management, moderate hypothermia using α -stat management was associated with a decrease in local CBF in all but five brain structures (cochlear nuclei, dentate nuclei, superior olive, internal capsule, medial habenulae).

Coupling of blood flow to metabolism

The coupling of CBF to cerebral glucose utilization was maintained during mild and moderate hypothermia with α -stat management as shown by the relationship of local cerebral glucose utilization in each of the 41 brain regions to the local CBF in the same regions (Fig. 3) ($P > 0.05$). During pH-stat management at 35°C and 32°C, the relationship

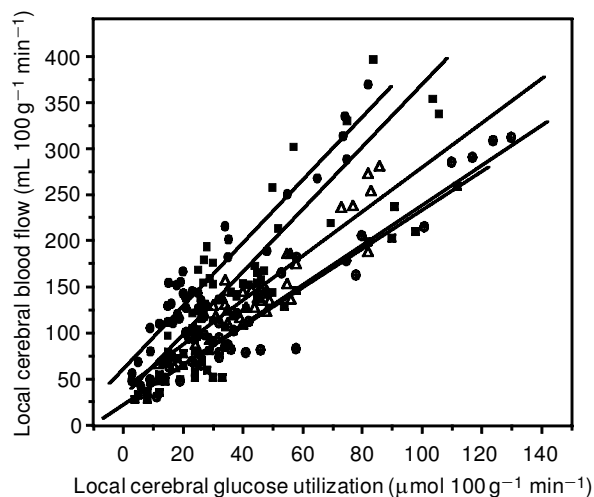


Figure 3.

Effects of the pH management during graded hypothermia on the coupling of cerebral glucose utilization with cerebral blood flow if either α -stat (\oplus (35°C) and \boxplus (32°C)) or pH-stat (\bullet (35°C) and \blacksquare (32°C)) management is used (with permission from [16,17]). The overall relationship between local cerebral glucose utilization (LCGU) and local cerebral blood flow (LCBF) in the examined structures of the brain was assessed by the least squares fit of the data to $y = ax + b$, where x is the mean LCGU in a given region, and y is the mean LCBF in that same area. Normothermic anaesthetized: $y = 2.4x + 37.9$, $r = 0.92$; α -stat 35°C: $y = 2.2x + 22.2$, $r = 0.95$; α -stat 32°C: $y = 2.1x + 26.4$, $r = 0.96$; pH-stat 35°C: $y = 3.4x + 31.6$, $r = 0.92$; pH-stat 32°C: $y = 3.4x + 62.4$, $r = 0.96$. Contrasts of slopes of the LCBF/LCGU regression lines were tested by common t -test statistics with Bonferroni correction for multiple comparisons ($P \leq 0.05$ between the slopes of the pH-stat groups vs. normothermia and pH-stat vs. α -stat, $P > 0.05$ between the slopes of the hypothermia groups at 35°C and 32°C and both α -stat groups vs. normothermia). Because of the limitations of this kind of analysis, an additional more rigorous statistical approach using log-transformed data was applied, examining the relationship of LCBF and LCGU by a repeated measure of the analysis of variance according to McCulloch et al. [23] and Ford et al. [24]. For this analysis, a computer software package (BMDP2v[®]; BMDP Statistical Software Inc., Los Angeles, CA, USA) considering inter-animal variability and enabling the detection of heterogeneities in the relationship between LCGU and LCBF was used.

between local CBF and local cerebral glucose utilization was preserved but was shifted to a higher level (Fig. 3) ($P \leq 0.05$). This means that, compared to normothermic anaesthesia, hypothermia and pH-stat management reduced the local CBF less than the local cerebral glucose utilization in a brain structure. During α -stat management, the relationship between local CBF and local cerebral glucose utilization is unchanged during hypothermia; this results in a reduction of local CBF in parallel to the local cerebral

glucose utilization. In conclusion, pH management increases mean and local CBF but does not uncouple CBF from metabolism. Only the relationship of CBF to cerebral glucose utilization is shifted to a higher level during pH-stat management.

Is acid-base management relevant for the design of studies on hypothermic neuroprotection?

Those results derived from experimental studies cannot be directly transferred to the clinical setting, because results were obtained from healthy animals without brain ischaemia or trauma. However, there remains the possibility that pH-stat may be superior to α -stat management for neuroprotection during moderate hypothermia: first, an abolished vessel reactivity to physiological stimuli appears only to occur in the ischaemic core whereas it wanes with distance in the perifocal area [18]. During the first hours, neuronal injury in this perifocal area is essentially reversible and may be salvageable. Therefore, preserved vascular reactions may, by vasodilatation, delay or even avoid the progressive metabolic deterioration of the penumbra and the enlargement of the dense ischaemia zone. Working on both metabolism increase and perfusion decrease, hypothermia should be better combined with an increase in CBF during pH-stat than the reduction observed during α -stat management. Another potential mechanism – in addition to better cerebral oxygenation – might be that an increased or maintained CBF itself might result in a more homogenous temperature profile throughout the brain [19] thus counteracting the considerable temperature gradient in ischaemic brain [20]. Moreover, it is well known that experimental hypothermic neuroprotection depends not only upon reduced metabolism but on several other factors such as the release of neurotoxic mediators or the integrity of the blood–brain barrier [21]. At least in modestly perfused tissues, e.g. the penumbra, one can speculate that these toxic mediators are eliminated more efficiently by a higher blood flow. On the other hand, a preserved or even an increased CBF has to be avoided so as not to reach a critically raised intracranial pressure (ICP). However, ICP elevations in brain trauma [4] and severe stroke [22] are less frequent during hypothermia than during normothermia.

In conclusion, pH management does not uncouple CBF from metabolism but pH-stat management shifts the relationship of CBF to cerebral glucose utilization to a higher level. Relevant clinical outcome studies on the effect of the acid–base management during hypothermia on ischaemia or brain injury are lacking. As long as they do not exist, the pH-management used in studies for neuroprotective

hypothermia needs to be carefully considered to avoid further controversial results.

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