Persistent Metabolic Disturbance in the Perihemorrhagic Zone Despite a Normalized Cerebral Blood Flow Following Surgery for Intracerebral Hemorrhage

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BACKGROUND: We hypothesized that reduced cerebral blood flow (CBF) and/or energy metabolic disturbances exist in the tissue surrounding a surgically evacuated intracerebral hemorrhage (ICH). If present, such CBF and/or metabolic impairments may contribute to ongoing tissue injury and the modest clinical efficacy of ICH surgery.

OBJECTIVE: To conduct an observational study of CBF and the energy metabolic state in the perihemorrhagic zone (PHZ) tissue and in seemingly normal cortex (SNX) by microdialysis (MD) following surgical ICH evacuation.

METHODS: We evaluated 12 patients (median age 64; range 26-71 yr) for changes in CBF and energy metabolism following surgical ICH evacuation using Xenon-enhanced computed tomography (n = 10) or computed tomography perfusion (n = 2) for CBF and dual MD catheters, placed in the PHZ and the SNX at ICH surgery.

RESULTS: CBF was evaluated at a mean of 21 and 58 h postsurgery. In the hemisphere ipsilateral to the ICH, CBF improved between the investigations (36.6 ± 20 vs 40.6 ± 20 mL/100 g/min; $P < .05$). In total, 1026 MD samples were analyzed for energy metabolic alterations including glucose and the lactate/pyruvate ratio (LPR). The LPR was persistently elevated in the PHZ compared to the SNX region ($P < .05$). LPR elevations in the PHZ were predominately type II (pyruvate normal-high; indicating mitochondrial dysfunction) as opposed to type I (pyruvate low; indicating ischemia) at 4 to 48 h (70% vs 30%) and at 49 to 84 h (79% vs 21%; $P < .05$) postsurgery.

CONCLUSION: Despite normalization of CBF following ICH evacuation, an energy metabolic disturbance suggestive of mitochondrial dysfunction persists in the perihemorrhagic zone.

KEY WORDS: Cerebral blood flow, Energy metabolism, Intracerebral hemorrhage, Microdialysis, Xenon-enhanced computed tomography

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Spontaneous, nonaneurysmal intracerebral hemorrhage (ICH) carries a 30-d mortality rate of 25% to 48%,[1] and <40% of survivor reach functional independence.[2] Despite refined stroke and neurocritical care (NCC) units, the case fatality rate has not markedly improved over the past decades.[2] Surgical evacuation of an ICH is commonly life-saving, particularly for lobar ICHs, although it has not convincingly shown a distinct clinical benefit, compared to the best medical treatment, on clinical recovery in a larger selection of ICH

ABBREVIATIONS: CBF, cerebral blood flow; **CPP,** cerebral perfusion pressure; **CT,** computed tomography; **CTP,** computed tomography perfusion; **GCS-M,** motor component of Glasgow Coma Scale; **ICH,** intracerebral hemorrhage; **ICP,** intracranial pressure; **LPR,** lactate/pyruvate ratio; **MD,** microdialysis; **MML,** mixed models linear; **NCC,** neurocritical care; **PET,** positron emission tomography; **PHZ,** perihemorrhagic zone; **rCBF,** regional cerebral blood flow; **ROI,** regions of interest; **SD,** standard deviation; **SNX,** seemingly normal cortex; **Xe-CT,** Xenon-enhanced computed tomography

TABLE 1. Patient Characteristics

Patient no.	Age (yr)	Co-morbidities	ICH size (mL)	Midline shift (mm)	GCS-M on arrival	NCC LOS (d)	GCS-M on departure	Outcome (mRS)
1	48	HT, CVL	57.4	11	5	7	5	4
2	55	HT	86.6	10	5	5	4	6
3	26	HT	64.2	9	5	9	6	3
4	62	0	24.7	3	5	6	4	4
5	68	HT, AF, VKA	89.5	9	5	5	3	4
6	51	HepB	81.4	5	5	5	5	LTF
7	67	HT, DM	44.1	9	5	7	5	LTF
8	52	HT	35.5	4	6	4	6	2
9	71	0	75.0	5	5	3	6	2
10	66	0	90.5	14	3	5	4	6
11	68	0	41.2	13	5	9	6	4
12	65	0	42.4	5	5	9	6	3

ICH, intracerebral hemorrhage; HT, hypertension, CVL, previous cerebrovascular lesion; AF, atrial fibrillation; VKA, vitamin-K antagonist (Warfarin) treatment; HepB, Hepatitis B; DM, diabetes mellitus; GCS-M, motor component of Glasgow Coma Scale score; NCC, neurocritical care; LOS, length of stay; mRS, modified Rankin Scale score assessed at 3 mo postsurgery; LTF, lost to follow-up.

patients.[3,4] The causes of the modest clinical efficacy of surgery are unclear. There is an immediate mechanical disruption of glial cells, neurons, and axons at ICH onset,[5] followed by a complex cascade of secondary injury factors, many of which remain unknown.[6] Plausibly, these persisting secondary injury processes are insufficiently attenuated by surgical removal of the blood clot. In addition, a persistent energy metabolic crisis[7] at time of regional hypoperfusion[8] in the tissue surrounding the ICH, the perihemorrhagic zone (PHZ), may be crucial. Clinically, the energy metabolism may be assessed using cerebral microdialysis (MD) for the analysis of the lactate/pyruvate ratio (LPR), reflecting the cytoplasmatic redox state. Increased LPR may be caused by ischaemia, named type I LPR elevation, and mitochondrial dysfunction, named type II LPR elevation.[9] The time course, type and extent of energy metabolic and blood flow disturbances in ICH remain to be established.[8, 10]

The aim of this study of surgically treated ICH patients was to investigate the energy metabolic situation in the PHZ compared to that in seemingly normal cortex (SNX) using dual MD catheters. In addition, cerebral blood flow (CBF) was evaluated at an early and late time point postoperatively. We hypothesized that surgical ICH removal is associated with an improved CBF and/or energy metabolism in the tissue surrounding the ICH.

METHODS

Study Design

Prospectively recruited spontaneous ICH patients, surgically treated between November 2014 and November 2016, were included. The Regional Ethical Committee approved the study. A written informed consent was obtained from the patient's closest relative.

Patient Characteristics and Management

Patients >18 yr old requiring surgical evacuation of supratentorial ICH, receiving dual cerebral MD catheters and repeated evaluation of CBF during NCC were conveniently recruited. Surgical and clinical decisions were made by the consultant neurosurgeon on a case-by-case basis. Candidates for surgical evacuation and/or intracranial pressure (ICP) monitoring were ICH patients showing impaired or deteriorating level of consciousness and a surgically accessible ICH. Exclusion criteria were age <18 yr old, coagulopathy, and when a next of kin could not be located. Patients who did not receive dual MD catheters or 2 CBF investigations were also excluded.

On admission, the clinical characteristics including the motor component of the Glasgow Coma Scale (GCS-M) score was noted (Table 1). For patients intubated at the referring hospital, the GCS-M preceding intubation was noted. Intubated patients were sedated using propofol (n = 12) and midazolam (n = 1) pre- and postoperatively.

All patients were operated by routine craniotomy using a free bone flap, followed by microneurosurgical evacuation of the blood clot. ICP monitoring was performed in 10 patients (Figure 1). Postoperatively, the patients were managed in the NCC unit with a standardized treatment protocol including monitoring of secondary insults such as increased ICP and reduced cerebral perfusion pressure (CPP).[11,12] ICP-monitoring was achieved using Neurovent-P parenchymal pressure monitoring device (Raumedic AG, Helmbrechts, Germany) or Bactiseal ventricular catheter (DePuy Synthes, Raynham, Massachusetts). Time to surgery was defined as time from known or presumed ictus to surgery.

Three months postoperatively, the modified Rankin Scale[13] was assessed using a questionnaire or a structured interview by telephone.

Neuroradiology and Blood Flow Measurement

The computed tomography (CT) scan preceding surgery was analyzed for midline shift (mm) and ICH volume, using the formula ($a \times b \times c/2$)[14]. All patients underwent a CT-angiography preoperatively.

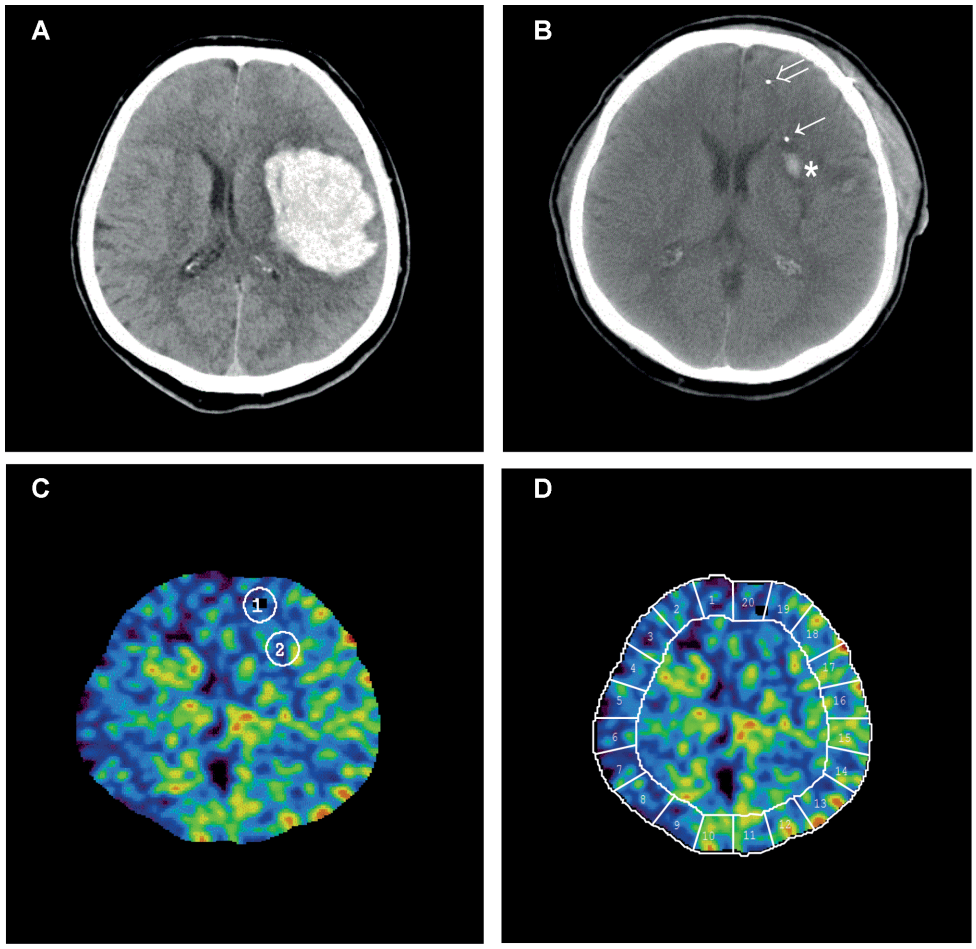

FIGURE 1. *Native and Xenon-enhanced CT-scan; evaluation of CBF and placement of MD catheters.* **A**, *CT scan of a 67-yr-old man with a large left-sided ICH in the basal ganglia, emergently treated surgically by craniotomy and open evacuation of the clot.* **B**, *Postoperative CT scan shows the location of the 2 MD catheters, one (→) in the PHZ in the vicinity of the hemorrhage cavity (*), the other in SNX (⇒open arrow).* **C**, *First postoperative Xe-CT CBF evaluation showing the hand-drawn ROI surrounding the MD catheters.* **D**, *The second Xe-CT CBF evaluation at 66 h postoperatively shows the 20 standardized cortical ROIs used in the present study.*

CBF was measured using Xenon-enhanced computed tomography (Xe-CT) according to locally adopted routines.[15,16] Xenon is a metabolically inert and readily diffusible tracer, safely used for CBF evaluations in NCC.[16,17] Patients underwent an early (day 0-2 postsurgery) and late (day 3-6 postsurgery) Xe-CT (CereTom 0-NL3000-001, Neurologica, Danvers, Massachusetts). A gas mixture of 28% Xenon was added during a 4.3 min long wash-in period to the ventilator air/O_2-mixture. The computer software (Diversified Diagnostic Products Inc, Houston, Texas) enabled the timed Xenon delivery. A standard 4-level Xenon-CT CBF exam using 10 mm spacing between levels (using 8 scans per level, 2 baseline and 6 enhanced) was used and CBF (mL/100 g/min) calculated from the tissue enhancement by the Xenon.[18,19] The CBF-values were visualized using a color-coded image (Figures 1C-1D).

A modified Kety–Schmidt method was used,[15,20] and mean cortical CBF for 20 evenly distributed regions of interest (ROI; Figure 1D) in each of the 4 levels were automatically calculated. The area of the MD catheters was identified on the structural CT and manually outlined (Figure 1C). This ROI was ≥200 mm^2 for robust mathematical CBF calculations.[19] At the time of Xe-CT CBF investigations, patients were sedated, ventilated, and physiologically monitored (Table 2). In 2 patients computed tomography perfusion (CTP) was used to estimate CBF, 1 due to obesity and 1 to early extubation.

CTP images were obtained according to clinical routine using a 128-slice CT scanner.[21,22] Iodinated contrast agent (45 ml; Joversol 350 mg/ml, Gothia Medical, Gothenburg, Sweden) was administered at a rate of 6 ml/s followed by a saline flush. Image acquisition was initiated 2 s after the start of the contrast injection. Quantitative perfusion data were obtained through repeated imaging of a 90 mm/84 mm slab of the brain during a 44/45 s time period, thus covering the first pass contrast inflow. Images were reconstructed into 10 mm thick slices and analyzed using a

TABLE 2. MD and CBF Characteristics

Pat. no.	Time from ictus to surgery (h)	Time from ictus to onset of MD sampling (h)	Duration of MD sampling (h)	Distance of PHZ-catheter to ICH (mm)	Time from surgery to CBF1 (h)	Time from surgery to CBF2 (h)
1	6	10	172	5	23	89
2	4	16	86	2	18	68
3	22	30	184	10	27	58
4	22	30	70	5	22	45
5	8	14	108	3	45	67
6	5	16	112	3	10	70
7	17	16	140	8	21	66
8	3	12	84	2	23	60
9	10	18	74	10	22	53
10	37	42	56	2	11	36
11	3	5	130	2	19	46
12	36	38	82	8	9	34

Pat, patient; h, hours; MD, microdialysis; PHZ, perihemorrhagic zone; ICH, intracerebral hemorrhage; CBF, cerebral blood flow
Pre: CBF estimation evaluated prior to surgery.

deconvolution-based algorithm. Perfusion data were presented as color-coded maps depicting CBF, cerebral blood volume, and mean transit time, with ROIs matching the Xe-CT investigations [21,22] and evaluated by a neuroradiologist blinded to the clinical data of each individual patient. CBF data were similar from Xenon-CT and CTP examinations and were pooled.

Microdialysis

At time of surgery, 1 MD catheter was placed adjacent (<1 cm) to the hematoma cavity (the PHZ). One control MD catheter was placed either via the craniotomy (n = 11) or a separate burr hole (n = 1) in the SNX of a noneloquent area. CMA 71 Brain MD Catheters, membrane length 10 mm and 100 kDa molecular weight cut-off (M Dialysis AB, Solna, Sweden) were used. The catheters are routinely, since 2013 in our department, perfused with a commercially available 5% human albumin solution to reduce fluid loss across the MD membrane[23,24] (Albunorm, Octapharma, Stockholm, Sweden) at a rate of 0.3 μL/min. After MD catheter insertion, 2 h passed before sampling was initiated. MD is used for clinical monitoring and to reduce the samples analyzed, vials are routinely collected on a 2-h basis instead of each hour in our unit.[23-25] Interstitial glucose, lactate, pyruvate, glycerol, and glutamate were analyzed bedside (ISCUSflex analyser; M-Dialysis AB). The LPR was calculated and urea monitored MD catheter performance.[26]

The following MD data were considered critical.[27] MD-glucose: <0.2 mmol/L critical and <0.8 mmol/L considered a warning sign; LPR > 40 critical and LPR > 25 a warning sign. The incidence of LPR elevations type I, indicating ischemia (defined as LPR > 25 or > 40 and pyruvate < 70 μmol/L)[28] was noted. The definition of type II LPR elevations, indicating mitochondrial disturbance, varies in the literature.[27,28] For the 2 type II LPRs (>25 and >40), 2 values for pyruvate (>70 μmol/L or >120 μmol/L) were also used, as previously suggested.[9,28,29] These calculations were performed on the first 4 to 84 h of MD sampling, and all analyses were performed by a researcher (L.T.) without the knowledge of the CBF data, and vice versa.

The distance from the MD catheter tip to the ICH cavity was measured on postoperative CT scan.

Statistical Methods

The target sample size was based on the only previous clinical ICH study where 2 MD catheters were used.[7] Due to the observed differences in the PHZ compared to putatively normal MD values observed in that study, and the complexity of the present study design, we aimed to include 18 patients expecting that some patients had to be excluded. SPSS Statistics 22 (IBM, Armonk, New York) was used. Paired *t*-test was used for normally distributed data and paired Wilcoxon rank test for nonnormally distributed data. Chi-square test was used for comparison of proportions. Correlation analysis was performed using Spearman's rank correlation of MD data to CBF.

PHZ and SNX MD data were compared using a mixed models linear (MML) approach, with catheter location as fixed effect and patients as subject level and random effect.[30] MML approach was also used for hemispheric CBF differences using hemisphere as fixed effect. A *P*-value < .05 was considered statistically significant.

Normally distributed data are presented as means ± standard deviation (SD), nonnormally distributed data as median and range. For clarity, MD data are presented using mean ± SEM.

RESULTS

Eighteen surgically treated ICH patients >18 yr old were recruited. Six patients were then excluded; 4 since a MD catheter malfunctioned, and 2 since CBF measurements could not be performed according to protocol. Thus, 12 patients were included.

Patient Characteristics and Radiology

Median patient age was 64 yr (range 26-71 yr; Table 1). Median GCS-M score on arrival was 5 (range 3-6; Table 1). Ten patients had a central ICH and 2 a lobar ICH. Hemorrhages were evacuated at a mean of 14 h (range 3-37) after ICH onset. Ten patients received ICP monitoring. Postoperatively, no patients experienced ICP-elevations requiring

ICP-lowering therapies such as decompressive craniectomy, hypertonic saline/mannitol, or barbiturates. The ICH and clinical characteristics are described in Table 1.

CBF Measurements

CBF measurements were performed 14.2 ± 24 h (Xe-CT 1) and 59.5 ± 19 h postsurgery (Xe-CT 2) in 10 patients. The 2 CT-perfusion studies were performed at 18 and 23 h (CTP 1) and 60 and 68 h postsurgery (CTP 2), respectively. ICP, CPP, MAP, pCO_2, pO_2, and the use of muscle relaxant, sedatives, and inotropic drugs remained stable during the CBF investigations and were similar between the first and second CBF study (Table 2).

Global CBF was 37.5 ± 21 mL/100g/min at CBF1, which improved to 40.1 ± 19 mL/100g/min at CBF2 ($P < .05$; Figure 2A). Regional cerebral blood flow (rCBF) was lower in the hemisphere harbouring the ICH than contralaterally (36.6 ± 20 vs 38.3 ± 21 mL/100g/min, respectively, $P < .05$; Figure 2A) at CBF1. At CBF2, there were no differences between the hemispheres (40.6 ± 20 and 39.6 ± 19 mL/100g/min, respectively; Figure 2A). In the MD catheter ROIs, the CBF was significantly lower in ROI_{PHZ} (25.7 ± 14 mL/100g/min) compared to in ROI_{SNX} (40.9 ± 20 mL/100g/min; $P < .05$; Figure 2B) at CBF1, but there was no statistically significant difference between these regions at CBF2 (36.5 ± 27 mL/100g/min in ROI_{PHZ} and 42.7 ± 30 mL/100g/min in ROI_{SNX}; $P = .426$).

MD Reveals a Persisting Energy Metabolic Disturbance in the PHZ Following ICH Surgery

In total, 6598 analyses in 1026 MD samples were performed (glucose, lactate, pyruvate, glycerol, and glutamate). The mean duration from ICH onset to start of MD sampling was 20.6 ± 12 h (range 5-94 h), and the mean duration of sampling was 108 ± 41 h (range 56-184 h; Table 3). Five vials of the 1026 were excluded due to deviating urea values.[26] The low-molecular weight analyses are shown in Figures 3A-3D. There was a significant difference between the PHZ and the SNX catheter for all metabolites except glycerol ($P < .05$; Figures 3A-3D). In the first 4 to 84 h, 48% of MD-Glucose levels in the PHZ were below <0.8 mmol/L and 9% < 0.2 mmol/L. In the SNX, 26% of MD-Glucose levels were <0.8 mmol/L although no sample was <0.2 mmol/L.

The MD-lactate levels were consistently higher ($P < .05$; Figure 3B) in the PHZ compared to the SNX, as was MD-glutamate ($P < .05$; data not shown). The MD-pyruvate levels were also higher in the PHZ compared to the SNX ($P < .05$; Figure 3C). There was no significant difference in MD-glycerol between sampled regions (not shown). The lactate/pyruvate ratio was consistently elevated in the PHZ compared to the SNX ($P < .05$; Figure 3D).

In the first 4 to 84 h, the LPR was >25 in 70% of all samples (298/424 samples) in the PHZ as compared to 23% (101/436 samples) in the SNX ($P < .05$). The LPR was >40 in 38%

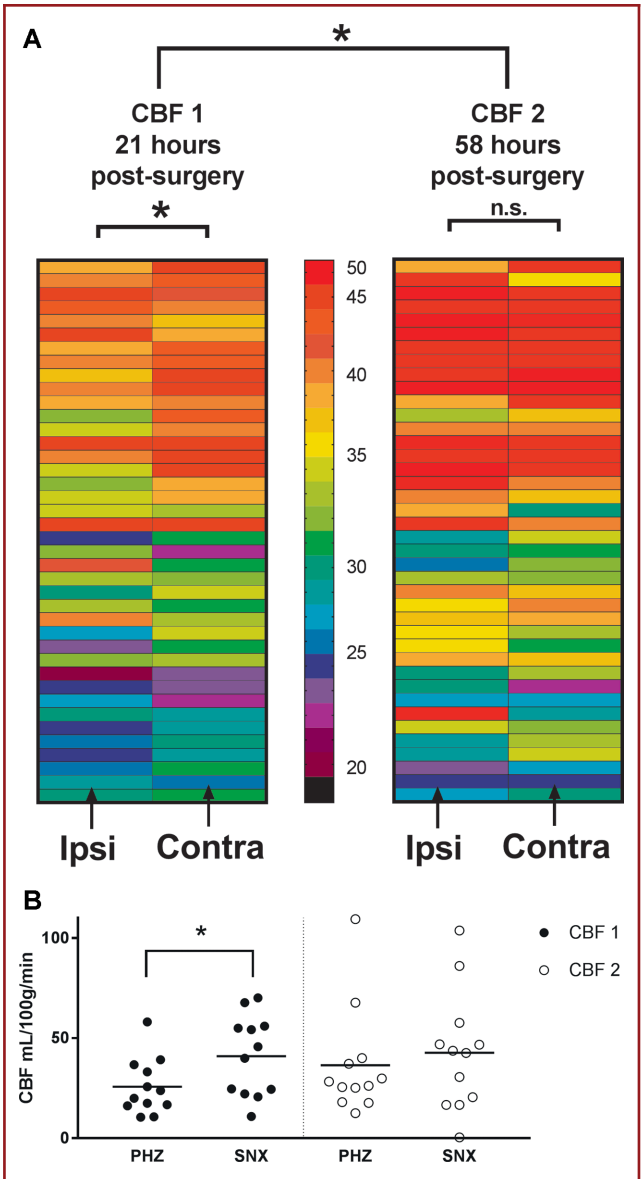

FIGURE 2. *CBF evaluated by Xenon-CT following surgical evacuation of ICH.* **A**, *Heat-map of 40 ROI in each hemisphere shows that CBF improved significantly (*) between the early (CBF1; 20.8 ± 10 h postsurgery) and late (CBF2; 57.7 ± 16 h postsurgery) globally. The CBF in the ipsilateral hemisphere was significantly lower (indicated by *) than in the contralateral hemisphere at the early (CBF1) postinjury time-point, but this difference was not present at CBF2. CBF improved significantly between CBF1 and CBF2 both in the ipsilateral hemisphere and contralateral hemisphere (P < .05 = *).* **B**, *CBF was lower in the local ROI centered on the MD catheter in the PHZ as compared to that of the SNX on the first CBF evaluation. At the second CBF evaluation, there was no difference in CBF between the ROIs in the SNX and PHZ. PHZ, perihemorrhagic zone; SNX, seemingly normal cortex; Ipsi, ipsilateral to the hemorrhage; Contra, contralateral to the hemorrhage; n.s., not significant.*

TABLE 3. Clinical Parameters at the Time of CBF-Measurement

Parameter	CBF1 (n = 12)	CBF2 (n = 12)	*P*-value
ICP (cmH_20; n = 10)	12.7 ± 6	13.7 ± 3	.96
CPP (mmHg; n = 10)	67.3 ± 10	73.4 ± 11	.33
MAP (mmHg)	86.6 ± 10	92.8 ± 12	.25
Propofol 20 mg/mL (mL/h)	15.3 ± 7	15.2 ± 8	.95
Remifentanil 100 μg/mL (mL/h)	5.0 ± 4	5.5 ± 4	.22
NE 40 μg/mL (mL/h)	7.2 ± 6	5.8 ± 4	.34
pCO_2 (kPa)	5.4 ± 0.3	5.3 ± 0.5	.13
pO_2 (kPa)	13.0 ± 2	14.2 ± 2	.39

ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP, mean arterial blood pressure; NE, norepinephrine; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen
All data presented as means ± SD. *P*-values from Student's *t*-test.

(163/424 samples) in the PHZ and 3% (14/472 samples) of all MD samples in the SNX ($P < .05$).

The definition of type II LPR requires normal or elevated pyruvate levels >70 μmol/L. Of note, in previous definitions of type II LPR elevations pyruvate levels either >120 μmol/L or >70μmol/L were used.[9,29,31,32] In our material, pyruvate levels >120 μmol/L were more common than 70 to 120 μmol/L in type II LPR elevations, presented in full detail in Figure 4A and 4B. In the following paragraph, all type II LPR elevations with pyruvate levels >70 μmol/L are reported.

In the PHZ at 4 to 48 h, of all samples with LPR > 25 (n = 190/255 samples), 30% had type I and 70% type II LPR elevation. In the PHZ at 49 to 84 h, of all samples with LPR > 25 (n = 108/169 samples), 21% had a type I and 79% type II LPR elevation ($P < .05$; Figure 4A). In the SNX at 4 to 48 hours, of all samples with LPR > 25 (n = 72/257), 58% had a type I and 42% had type II LPR elevation. In the SNX at 49 to 84 h, of all samples with LPR > 25 (n = 29/179 samples), 62% had a type I and 38% had a type II LPR elevation ($P < .05$; Figure 4A).

In the PHZ at 4 to 48 h, of all samples with LPR elevations >40 (n = 103/255), 41% had type I and 59% a type II LPR elevation. In the PHZ at 49 to 84 h, of all samples with LPR > 40 (n = 60/169 samples), 32% had a type I and 68% a type II LPR elevation. In the SNX at 4 to 48 h, LPR was >40 in only 5 of 257 samples, of these 60% had a type I and 40% had a type II

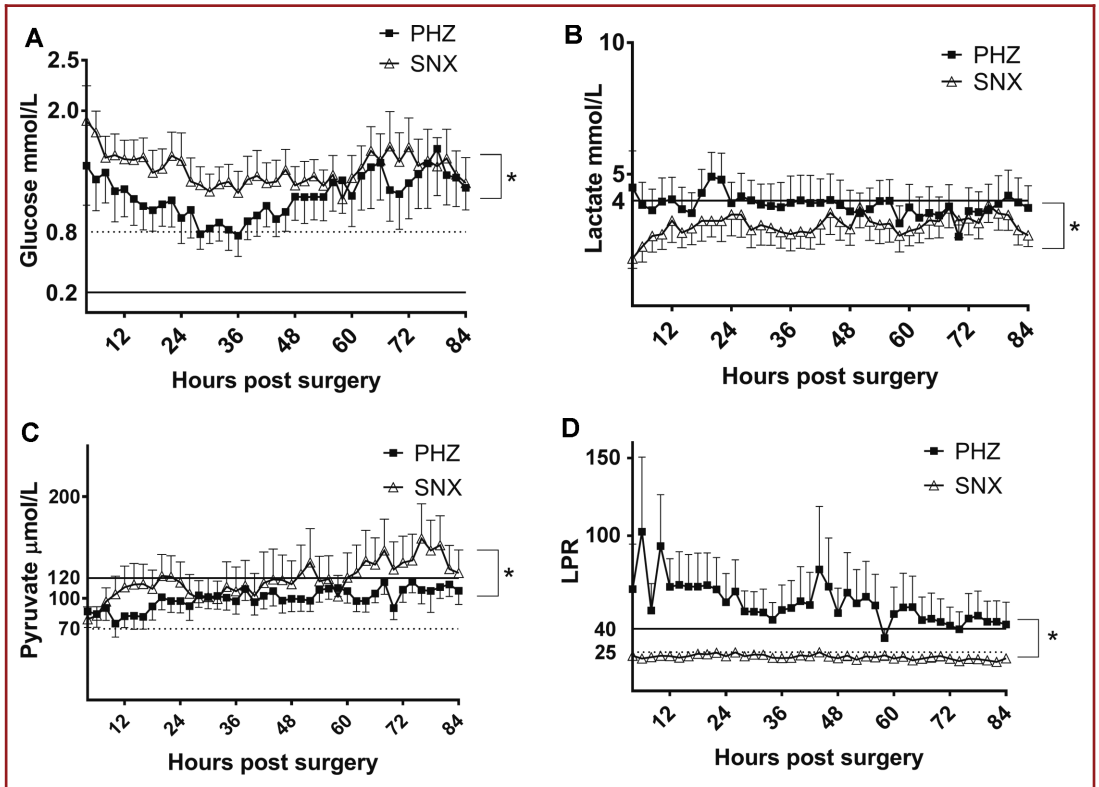

FIGURE 3. *Energy metabolic disturbance in the PHZ evaluated by MD following surgery for ICH. MD analyses for the first 4 to 84 h postsurgery of the MD samples obtained from the PHZ and SNX.* **A-D**, *Results for glucose, lactate, pyruvate, and the LPR are shown. The MD-glucose levels* **A** *were consistently lower while the MD-lactate levels* **B** *and MD-pyruvate levels* **C** *were consistently higher in the PHZ compared to the SNX (P < .05).* **D**, *The LPR in the PHZ was markedly elevated, the mean ratio being consistently higher when compared to the SNX (*P < .05).*

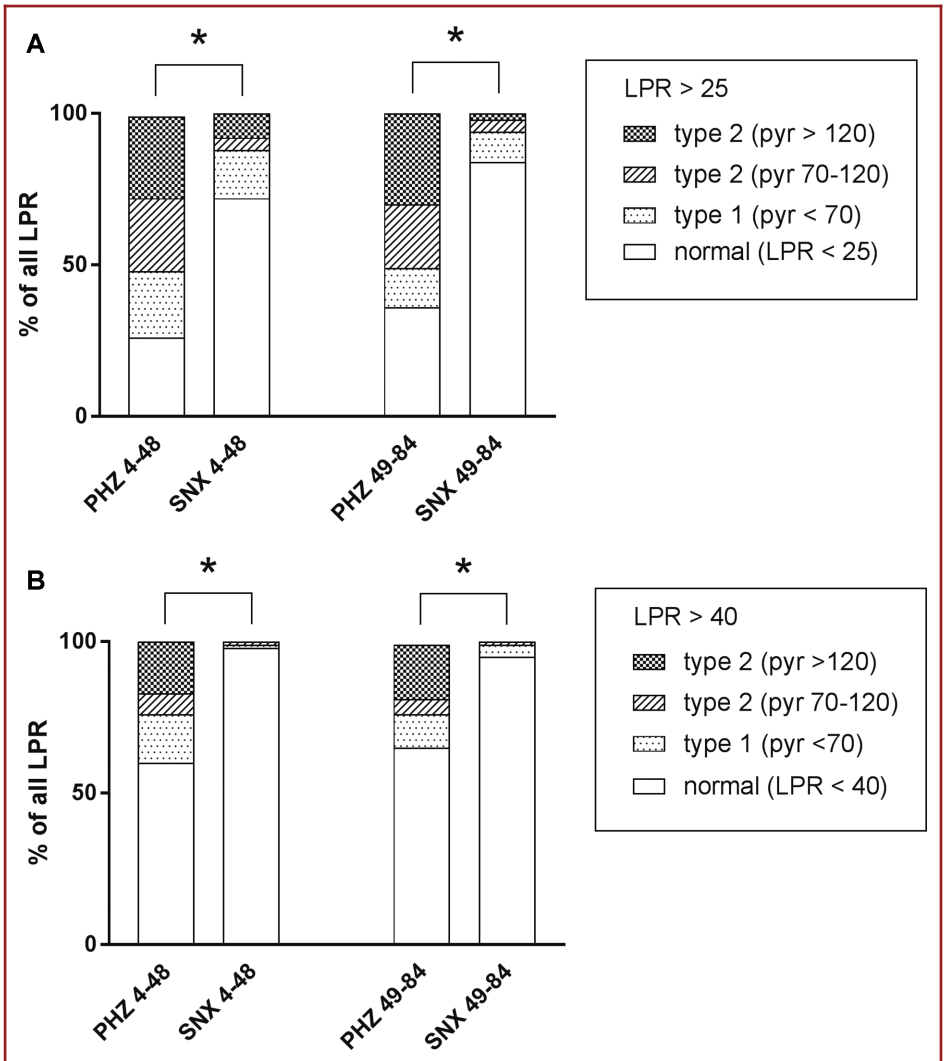

FIGURE 4. *LPR elevations in the PHZ following surgical evacuation of ICH. Based on available literature and recommendations, a LPR elevation in MD samples may be defined as >25* **A** *or >40* **B**. *In addition, a type I LPR elevation (defined as an LPR elevation and pyruvate levels <70 μmol/L) indicates an ischemic situation, and a type II LPR elevation (defined as an LPR elevation and pyruvate level being either 70-120 or >120 mmol/L*[9,28,29,31,54,55]*) indicates mitochondrial dysfunction.* **A**, *When comparing the LPR elevations, here defined as an LPR > 25, obtained from MD catheters placed in the PHZ, the incidence of type I LPR and particularly type II LPR was higher than the values from MD catheters placed in SNX early (4-48 h) following ICH surgery. At the late postsurgery time-points (48-84 h) the energy metabolic disturbance persisted in the PHZ, although less pronounced than at the early time point. The majority of these LPR elevations were of type II, indicating persisting mitochondrial disturbance.* **B**, *Less MD samples met the criteria for type I and type II LPR elevations when an LPR > 40 was used as a cut-off. Still, both type I and type II LPR elevations were observed with similar relative frequencies observed when LPR > 25 was used as a cut-off. pyr, pyruvate; P < .05 between groups at both LPR > 25 and LPR > 40.*

LPR elevation. At 49 to 84 h in the SNX, 9 of 179 samples had an LPR > 40 and of these, 89% had a type I and 11% had a type II LPR elevation ($P < .05$; Figure 4B).

There was no correlation between CBF and LPR analyzed in time periods of 2, 4, 6, or 10 h prior to CBF investigation (data not shown).

DISCUSSION

The present study, the first to use dual MD catheters combined with repeated evaluations of CBF, shows a persisting energy metabolic disturbance in the brain tissue surrounding a surgically evacuated intracerebral hemorrhage (ICH) despite a

normalization of CBF. Moreover, the pattern of LPR elevations indicates a persistent mitochondrial disturbance.

CBF Changes Following ICH Surgery

Most rCBF levels were higher than those typically associated with ischemia, both in the ipsilateral hemisphere and in the PHZ. Furthermore, an improved CBF ipsilateral to the evacuated hematoma was observed between the 2 CBF studies, conducted at 21 and 58 h postsurgery. We cannot exclude that time to ICH removal, which varied among the patients, influenced the CBF values. In nonevacuated ICH, a hypoperfusion zone surrounding the hemorrhage was observed in both the experimental[33-36] and clinical setting.[37-39] Using positron emission tomography (PET), the PHZ displayed a reduced CBF up to 43 h postictus,[40] although not reaching ischemic levels.[38,40,41] Additionally, no evidence of PHZ ischemia was observed in conservatively treated ICH patients using magnetic resonance spectroscopy.[37] Although no CBF studies comparing surgically and conservatively treated ICH patients over time are available, previous experimental and clinical studies report an improved CBF following ICH removal, [35,42-44] implying that surgical blood clot removal aids in restoring CBF. In conservatively treated ICH patients, a varying pattern of initial hypoperfusion was coupled to hypometabolism in the PHZ.[37,38,44-48] Although some reports show a gradual normalization of CBF over time,[8] others show a variable decrease.[40,44,45,47,48] For clinical reasons, we used 2 techniques for investigating CBF, Xe-CT in 10 and CTP in 2 patients, with good correlation between these methods.[49,50] Since CTP determines only relative, not absolute CBF, it was used here only when Xe-CT could not be performed.

Energy Metabolic Disturbances in Brain Tissue Following ICH Surgery

An ICH may be surrounded by a potentially salvageable PHZ different from the penumbra of ischemic stroke, in which the supply of oxygen and substrate is sufficient for cell survival although insufficient for normal neuronal activity.[51] Although there was gradual improvement of MD glucose, lactate, and the LPR, normalization did not occur suggesting a pattern of persistent metabolic impairment in the PHZ, evident by an elevated LPR. In a previous study, 1 to 3 PHZ MD catheters were used and the immediate LPR increase following ICH surgery gradually normalized, similarly to our results. Glucose levels were normal, whereas pyruvate levels were not presented.[7] In addition, CBF was not evaluated and no distinction between type I and II LPR elevations was made.[7] Similar to traumatic brain injury,[9,52] subarachnoid hemorrhage[28] and bacterial meningitis patients,[32] the LPR elevations observed in the present study suggest a mitochondrial dysfunction, which could contribute to the rather modest motor improvement observed postsurgery in our cohort.

There are no established criteria for type I or type II LPR elevations. Based on available literature, we used 2 different LPRs as well as pyruvate levels, based on the suggested reference pyruvate values (166 $\pm$ 47 μmol/L).[9,28,29,31,32,53-55] Regardless of the definition, the PHZ displayed higher LPRs, mainly type II, than the SNX. In contrast, glucose levels were above critical thresholds indicating sufficient substrate delivery. We cannot exclude that the surgical approach contributed to the suggested mitochondrial dysfunction since no nonsurgical control group was available. However, our data support previous work using PET-studies obtained 5 to 22 h after ICH onset, and work using a single perioperative biopsy, obtained at 6 to 72 h in 6 patients, showing reduced oxygen extraction fraction, hypometabolism, and mitochondrial dysfunction in the PHZ.[38,45,56] Persisting mitochondrial dysfunction with a reduced capacity for ATP generation may cause ongoing exacerbation of the ICH-induced tissue injury in the PHZ, as suggested by studies in traumatic brain injury,[57] and be an important secondary injury factor leading to delayed neuronal necrosis and/or apoptosis. Presumably, many factors contribute to mitochondrial dysfunction although complex metabolomics alterations could not be assessed using the present methodology. A few studies have evaluated possible treatment options for mitochondrial dysfunction in acute brain injury, including administrating succinate to the damaged tissue[58] or treating patients with suggested mitochondrial dysfunction with cyclosporine A,[59] hyperbaric oxygen,[60] or lactate, [61] interesting also for future ICH studies.

Study Limitations

The present data are based on a relatively small number of patients, included at a variable time point after ICH onset, and with a variable ICH location and volume. Since MD cannot be used in conservatively treated patients, we compared the energy metabolic situation in the PHZ with that in normal cortex. Although the control MD catheter was aimed at an area distant from the PHZ, preoperative pressure caused by ICH may have influenced the MD values of the SNX. Most devices for ICP monitoring were inserted ipsilaterally, and a separate burr hole solely for MD insertion could not be justified. No preoperative CBF measurements could be obtained and both the ICH itself and the surgery may have contributed to our results. Also, the small sample size did not allow us to evaluate any potential differences in CBF and metabolic disturbances across age groups or between patients with deep vs lobar hemorrhages.

MD monitors a $\sim$2 cm^3 brain region,[62] and the MD catheters were placed at a predefined location. Since all PHZ MD catheters were within 10 mm of the ICH, the influence of variations in MD catheter positioning on our results was presumably minor. Since the tissue injury imposed by the surgical approach may influence CBF and/or MD values, we cannot establish whether the observed CBF changes was caused by the surgical manipulation needed for ICH removal per se or merely reflected its natural course. Although no patient suffered from increased ICP postoperatively, we cannot exclude that preoperative ICP elevations resulted in persisting changes in CBF and/or MD results. Finally, the MD

results could have been influenced by the variable time from ICH onset to initiation of sampling.

CONCLUSION

Our data show that global and hemispheric CBF was gradually normalized following surgical evacuation of ICH. However, despite improved CBF a pattern of energy metabolic disturbance suggestive of mitochondrial dysfunction persisted in the PHZ. This may indicate that secondary pathological cascades triggered by the blood and/or the surgical trauma result in an ongoing energy metabolic crisis. Future studies are needed to determine if an earlier ICH evacuation could help restore the energy metabolic situation. Since it is plausible that surgical ICH removal contributes to improved CBF, future therapies may aim to target the mitochondrial dysfunction persisting in surgically treated ICHs.

Disclosures

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COMMENTS

The clinical benefit of evacuation of ICH has been difficult to show. The authors have investigated whether reduced CBF and/or metabolic energy disturbances exist in the tissue surrounding a surgically evacuated ICH. CBF was measured using xenon-enhanced CT or CT perfusion, and metabolic state was measured using dual microdialysis probes, 1 in the perihemorrhagic zone and 1 in presumed normal tissue. The authors conclude that CBF is normalized following ICH evacuation, whereas a metabolic energy disturbance suggestive of mitochondrial dysfunction persists in the perihemorrhagic zone. Although the series is relatively small and heterogeneous, the data set add some information on the pathophysiological mechanisms of brain damage after spontaneous ICH. Since there is no control group, for good reasons, the effect of surgery on the observed changes is, however, still uncertain.

One of the main reasons to evacuate an ICH is to prevent secondary injury in the penumbral area around the hematoma. Since CBF was normalized whereas a metabolic energy disturbance persisted after evacuation, future studies should aim at investigating whether there is a time window for evacuation that will increase the probability of restoring the metabolic state. The slight improvement in both glucose, lactate, and LPR in the perihemorrhagic zone over time although normalization was not reached, may indicate that earlier surgical intervention can improve the metabolic state in the perihemorrhagic zone.

Jon Berg-Johnsen
Oslo, Norway

The authors offer a manuscript describing the results of a prospective study of cerebral blood flow measurements via Xenon CT and cellular energy metabolism via microdialysis (MD) in patients undergoing open surgical evacuation of ICH. While this study is small, it is well designed and provides valuable prospective paired data on the state of brain CBF and metabolism in the initial postoperative period as well as in a delayed fashion after surgery. The study is enhanced by having MD data from both the perihemorrhagic zone as well as from seemingly normal brain cortex. The authors conclude that while surgery seemingly restores CBF, metabolic derangement in the tissue persist for at least a few days postoperatively. I think this study is particularly timely with recent trends in minimally invasive ICH evacuation, and while it involves maximally invasive craniotomies, I think the data can be applied to more recent

surgical trends. This study will lay the groundwork for future studies of CBF and metabolism in surgically vs conservatively managed ICH patients.

Joshua Osbun
St. Louis, Missouri

The authors should be congratulated, for this elegant microdialysis study, which makes 2 novel contributions… First, It offers new insight into the reasons why patients do not seem to robustly improve after removal of intracerebral hemorrhage, and second it shows the potential of intracerebral microdialysis to uniquely provide hard neurochemical evidence of metabolic changes in the living human brain. Several authors have documented CBF reduction in the perihemorrhagic zone around an intracerebral hematoma, to accord with neuropathological studies showing a zone of ischemic neuronal death, and damage, up to 1–2 cm around the clot.[1,2] This study however, suggests a larger zone of perihemorrhagic mitochondrial *functional* impairment, involving fairly large areas of the ipsilateral cortex, which persists several days after clot removal, and which offers a reason for the ongoing edema, (therefore mostly cytotoxic) and persisting neurological impairment usually seen in these patients postoperatively. Most importantly, however this study raises the possibility of treatments aimed at optimizing mitochondrial function, such as delivering more oxygen, or fuels such as lactate, succinate, or oxaloacetate, combined with clot removal surgery.

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