CBF changes and cerebral energy metabolism during hypervolemia, hemodilution, and hypertension therapy in patients with poor-grade subarachnoid hemorrhage

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OBJECTIVE Despite the multifactorial pathogenesis of delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH), augmentation of cerebral blood flow (CBF) is still considered essential in the clinical management of DCI. The aim of this prospective observational study was to investigate cerebral metabolic changes in relation to CBF during therapeutic hypervolemia, hemodilution, and hypertension (HHH) therapy in poor-grade SAH patients with DCI.

METHODS CBF was assessed by bedside xenon-enhanced CT at days 0–3, 4–7, and 8–12, and the cerebral metabolic state by cerebral microdialysis (CMD), analyzing glucose, lactate, pyruvate, and glutamate hourly. At clinical suspicion of DCI, HHH therapy was instituted for 5 days. CBF measurements and CMD data at baseline and during HHH therapy were required for study inclusion. Non-DCI patients with measurements in corresponding time windows were included as a reference group.

RESULTS In DCI patients receiving HHH therapy (n = 12), global cortical CBF increased from 30.4 ml/100 g/min (IQR 25.1–33.8 ml/100 g/min) to 38.4 ml/100 g/min (IQR 34.2–46.1 ml/100 g/min; p = 0.006). The energy metabolic CMD parameters stayed statistically unchanged with a lactate/pyruvate (L/P) ratio of 26.9 (IQR 22.9–48.5) at baseline and 31.6 (IQR 22.4–35.7) during HHH. Categorized by energy metabolic patterns during HHH, no patient had severe ischemia, 8 showed derangement corresponding to mitochondrial dysfunction, and 4 were normal. The reference group of non-DCI patients (n = 11) had higher CBF and lower L/P ratios at baseline with no change over time, and the metabolic pattern was normal in all these patients.

CONCLUSIONS Global and regional CBF improved and the cerebral energy metabolic CMD parameters stayed statistically unchanged during HHH therapy in DCI patients. None of the patients developed metabolic signs of severe ischemia, but a disturbed energy metabolic pattern was a common occurrence, possibly explained by mitochondrial dysfunction despite improved microcirculation.

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KEYWORDS subarachnoid hemorrhage; delayed cerebral ischemia; cerebral blood flow; hypertension, hypervolemia, and hemodilution therapy; triple-H; xenon CT; cerebral microdialysis; vascular disorders

DELAYED cerebral ischemia (DCI) is a common complication in the acute course of severe subarachnoid hemorrhage (SAH) and contributes substantially to mortality and long-term morbidity in this group of patients.^{6,33} The modern understanding of DCI is that the causes are multifactorial, with vasospasm as one of

many contributing factors. The process starts already at the aneurysm rupture and ictus of intracranial hypertension, causing global ischemia and early brain injury, and is then further escalated by degradation products from the clot, inflammatory response, microthrombosis, and microcirculatory disturbances.¹⁸ Aside from nimodipine, no spe-

ABBREVIATIONS ACA = anterior cerebral artery; CBF = cerebral blood flow; CMD = cerebral microdialysis; CPP = cerebral perfusion pressure; DCI = delayed cerebral ischemia; GCS = Glasgow Coma Scale; HHH = hypervolemia, hemodilution, and hypertension; ICP = intracranial pressure; L/P = lactate/pyruvate; MAP = mean arterial pressure; MCA = middle cerebral artery; NIC = neurosurgical intensive care; PCA = posterior cerebral artery; rCBF = regional CBF; ROI = region of interest; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure; TBI = traumatic brain injury; XeCT = xenon-enhanced CT.

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cific pharmacological treatment has proven to reduce the incidence of DCI or improve outcome.²

Compromised cerebral blood flow (CBF) may, by itself, contribute to the progression of DCI, and augmentation of CBF is considered essential in the management of patients suspected of having DCI.^{4,33} The concept of hemodynamic augmentation of CBF originally included hypervolemia, hemodilution, and hypertension (HHH) therapy to improve systemic blood flow and cerebral perfusion pressure (CPP), and to optimize blood rheology.^{15,23} Prophylactic use of HHH has been abandoned as the side effects might worsen outcome.^{8,17} However, it is established that ensuring normovolemia and normotension reduces the risk of DCI.^{19,20} Therapeutic use of HHH at suspicion of DCI has been addressed in several small and uncontrolled studies, but the results are divergent and there is no clear evidence concerning the effects of the different elements of HHH.⁵ Most guidelines now recommend only blood pressure augmentation, which is still based on weak scientific evidence.^{7,32}

When DCI is suspected in patients with SAH at our unit, our standardized neurosurgical intensive care (NIC) protocol includes careful application of HHH therapy with a moderately increased blood pressure target and vigilant hemodynamic reevaluation to minimize side effects. In a previous observational study at our institution, using xenon-enhanced CT (XeCT), CBF increased during HHH therapy,⁹ but there are still uncertainties regarding whether this leads to increased oxygen delivery in cerebral regions at risk and restoration of cellular energy metabolism. To our knowledge, there are few studies combining repeated measurement of CBF and continuous monitoring of cerebral energy metabolism in poor-grade SAH patients.^{24,29} Therefore, additional studies on the effects of therapeutic interventions to resolve DCI in these patients may provide valuable information.

The aim of this prospective observational study was to investigate cerebral metabolic changes in relation to CBF during HHH therapy at suspicion of DCI in patients with poor-grade SAH. CBF was assessed by bedside XeCT and the cerebral metabolic state by cerebral microdialysis (CMD). The primary hypothesis was that the cerebral metabolic state improves as CBF increases during HHH therapy, i.e., a less ischemic CMD pattern with decreased lactate level and lactate/pyruvate (L/P) ratio.

Methods

Patients

The study was conducted in a cohort of patients with severe spontaneous SAH, verified by CT, who had CBF measured by XeCT during their early acute course in NIC at Uppsala University Hospital from 2013 to 2016. All patients were on mechanical ventilation at the time of inclusion due to their initial level of consciousness or early neurological deterioration. CBF measurement using XeCT in our setting is only performed in intubated patients, which was thus a criterion for inclusion. Criteria for exclusion were pronounced intracranial hypertension, deep barbiturate sedation, inspired oxygen demand > 60%, inability to obtain consent from the patient's next of kin, and decisions

to withhold treatment. The study protocol was approved by the Uppsala University Regional Ethical Review Board and informed consent was obtained from the patients included or their next of kin. The study was also approved by the local radiation safety authority.

Study Design

Following our clinical NIC routine, intubated SAH patients should have XeCT CBF measurements at days 0–3, 4–7, and 8–12 if logistically possible. For the present study of cerebral energy metabolism in relation to CBF during HHH therapy, patients who had been examined with XeCT and who had a CMD catheter inserted at the same procedure as ventriculostomy were included. Data from CBF measurements and CMD, as well as clinical and physiological data, were prospectively collected. The neurological state of the patients was repeatedly evaluated. If the patient was determined to have a clinical diagnosis of DCI, HHH therapy was initiated in accordance with our standard NIC protocol as described below. To study the effects of HHH therapy, a baseline measurement of CBF was required within 48 hours before the start of HHH, and a second measurement was required during the 5-day course of the therapy. As a reference group, patients with CBF measurements at corresponding time windows but with no suspicion of DCI were identified.

XeCT for Measurement of CBF

In our NIC unit, assessment of CBF in mechanically ventilated patients is provided by bedside XeCT, following the principles originally developed by Gur et al. and Yonas et al.^{11,34} The inert xenon gas dissolves readily in blood and tissues, and acts as a radiographic contrast agent due to its high atomic number. Hence, inhaled nonradioactive xenon serves as a diffusible tracer during a repeated series of 4 axial CT scans and allows CBF to be calculated based on the Fick principle as applied by Kety for inert gas uptake in tissue.¹⁶ Xenon (28% in air/oxygen) is administered to the patients' breathing circuit by a computer-controlled delivery system (Enhancer 3000, Diversified Diagnostic Products Inc.), while synchronized CT scans are acquired by a mobile CT scanner (CereTom, Neurologica). CBF in each CT pixel is calculated by the integrated software, and finally mean blood flow is routinely calculated for each of 20 regions of interest (ROIs) defined in the CT images at three scan levels (Fig. 1A). ROIs in areas of hematoma or containing radiological artifacts are manually excluded.

Calculated CBF Parameters From XeCT

Global cortical CBF (ml/100 g/min) was calculated as the mean (weighted by ROI size) of all ROIs at all scan levels, typically a total of 60 ROIs. Regional CBF of the worst vascular territory (rCBF worst, ml/100 g/min) was identified for each patient and calculated as the mean of the corresponding cortical ROIs at all scan levels: anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories of the right and left hemisphere, respectively (Fig. 1A).

To quantify the distribution of areas with critically low and near-ischemic blood flow, thresholds for local CBF

FIG. 1. Example of an XeCT image with 20 cortical ROIs symmetrically set out (**A**), and an ROI set at the CMD catheter area (**C**, circle). The CMD ROI area was 509 mm², and the rCBF was 35.9 ml/100 g/min. The ventriculostomy catheter is also visible in the CT image (V-cath; **B**). The main vascular territories were approximated to the corresponding ROIs in each hemisphere.

were set to 10 and 20 ml/100 g/min.^{1,10} The proportion of cortical ROI area with local CBF below the specified thresholds was calculated as the sum of ROI area (mm²) with local CBF below the threshold divided by the total analyzed ROI area in each patient. Regional CBF of the CMD catheter ROI area (rCBF CMD, ml/100 g/min; Fig. 1B) was calculated from an ROI (approximately 500 mm²) manually set out in the XeCT image at the location of the tip of the CMD catheter (Fig. 1C).

Cerebral Microdialysis

The technique for CMD is well established in NIC for assessment of the metabolic state of the brain by measurement of interstitial glucose, lactate, pyruvate, and glutamate equilibrated to a microdialysis perfusion fluid circulated through a semipermeable microcatheter.^{12,13,21} As a routine clinical procedure in patients with severe SAH, a CMD catheter is placed in the cortex of the right frontal lobe at the same procedure as the insertion of a ventriculostomy catheter. For logistic and technical reasons, not all intubated SAH patients received CMD catheters. The CMD catheter used was the 70 Brain Microdialysis catheter (M Dialysis AB), with a 20-kDa cutoff membrane of 10-mm length. Artificial “cerebrospinal fluid” was perfused through the catheter at a rate of 0.3 µl/min using a microinjection pump (CMA-106, M Dialysis AB). The fluid had a composition of NaCl 147 mmol/L, KCl 2.7 mmol/L, CaCl₂ 1.2 mmol/L, and MgCl₂ 0.85 mmol/L (Perfusion Fluid CNS, M Dialysis AB). Hourly CMD samples were collected and analyzed at bedside using the CMA600 or the ISCUSflex Microdialysis Analyzer (M Dialysis AB). The level of CMD urea was monitored for validation of catheter performance.²⁵

CMD Parameters and Classification of CMD Metabolic Patterns

For this study, the means of CMD measurements (glucose, lactate, pyruvate, and glutamate) for 2 hours before and 2 hours after the XeCT CBF measurements were used. The L/P ratio was calculated for each CMD sample. In a consensus report from 2015, critical levels of these CMD

parameters were defined as glucose < 0.2–0.8 mmol/L, lactate > 4 mmol/L, and L/P ratio > 25–40.¹³

Additionally, the consensus report states that a pattern of increased L/P ratio and low pyruvate (in combination with low brain tissue oxygen if available) suggests an ischemic energy crisis, whereas a pattern of increased L/P ratio and normal/high pyruvate (in combination with normal brain tissue oxygen if available) suggests a non-ischemic energy crisis (e.g., mitochondrial dysfunction).¹³ In two recent studies on NIC patients with severe SAH¹⁴ and severe traumatic brain injury (TBI),²² cerebral ischemia was defined as an L/P ratio > 30 and pyruvate < 70 µmol/L, and cerebral mitochondrial dysfunction as an L/P ratio > 30 and pyruvate > 70 µmol/L. Based on these statements and studies, three patterns of the CMD parameters were defined to reflect the cerebral energy metabolic state of each patient in this study: normal (lactate < 4 mmol/L, L/P ratio < 30), mitochondrial dysfunction (L/P ratio > 30, pyruvate > 70 µmol/L), or ischemia (L/P ratio > 30, pyruvate < 70 µmol/L).

Finally, CMD glutamate was used as a biomarker of excitotoxicity, implicated as a secondary injury mechanism in SAH.¹³ The critical level of CMD glutamate was considered to be > 15 µmol/L, based on a previous SAH study.³¹

NIC of SAH Patients

SAH patients admitted to our unit are managed in accordance with a standardized NIC protocol for SAH, as described by Ryttefors et al.,²⁷ including multimodal monitoring of physiological and biochemical parameters and vigilance for avoidable factors to minimize secondary brain injury. Sedation is titrated with propofol (Frese-nius Kabi AB) 0–4 mg/kg/hr and morphine (Meda AB) as needed. In patients with altered levels of consciousness or hydrocephalus, an external ventricular drain is placed for intracranial pressure (ICP) monitoring and CSF drainage. ICP exceeding 20 mm Hg is treated with open ventricular drainage set at a pressure level of 15 mm Hg. Aneurysms are, as a rule, treated early, preferably with endovascular coil embolization when feasible, or with surgical clipping

TABLE 1. Characteristics for the group with a clinical diagnosis of DCI who subsequently received HHH therapy, and the reference group (non-DCI patients) with CBF measurements at corresponding time windows

Characteristic	DCI (HHH therapy)	No DCI (ref group)
No. of patients	12	11
Female/males	10/2	9/2
Mean age, yrs (range)	62 (48–75)	58 (28–84)
Treatment modality		
Endovascular	12	7
Surgical clip	0	4
CT Fisher grade		
3	5	2
4	7	9
Hunt & Hess grade		
At admission		
I–III	8	3
IV–V	4	8
At baseline XeCT		
III	3	4
IV–V	9	7
Clinical neurological course at NIC discharge		
GCS motor score 6	7	9
GCS motor score ≤5	5	2*
Infarct >20 mm at CT, day ≥12		
Yes	2	4
No	10	7

Ref = reference.

* One patient in the reference group died on day 11 in the NIC.

if indicated. The target for systemic volume status is normovolemia to mild hypervolemia if not contraindicated by cerebral edema or hematoma with mass effect and/or elevated ICP. To ensure volume status, fluids are administered in the higher normal range and patients are monitored by central venous pressure, clinical evaluation, and attentive fluid balance calculation. Albumin infusion (200 mg/ml, Baxter AG) is used for further volume expansion if needed. Mean arterial pressure (MAP) is kept above 85 mm Hg, and if vasoactive support is required, dobutamine (Hospira) is used as first-line and norepinephrine (Hospira Nordic AB) as second-line treatment. Nimodipine (Bayer Pharma AG) is routinely given from admission onward.

Diagnosis of DCI and HHH Therapy

The patients with SAH are repeatedly evaluated for neurological deterioration, and in cases of new focal deficits or reduced levels of consciousness, DCI is clinically diagnosed if other causes for deterioration are ruled out. In addition to standard therapy, HHH therapy to augment CBF is then initiated for 5 days with daily infusions of 500 ml dextran-40 solution (100 mg/ml, Meda AB) and 200 ml albumin (200 mg/ml). During HHH therapy, the pa-

tient is kept supine and the focus is on ensuring adequate intravascular volume status, while the blood pressure target is moderately elevated with a lower limit for systolic blood pressure (SBP) of 140 mm Hg. As described above, the first choice of vasoactive support is dobutamine and/or the addition of norepinephrine if needed. The neurological and hemodynamic situation is repeatedly reevaluated to minimize the risk of serious side effects.

Statistical Methods

SPSS statistical software (version 23.0, IBM Corp.) was used for statistical analyses of the collected data. Differences in systemic physiological parameters between measurements were tested by paired samples t-test. CBF and CMD data for groups of patients are presented as median values and IQR because of non-normal distribution. Differences in CBF and CMD parameters between related samples were tested by Wilcoxon signed-ranks test, and between independent samples by Mann-Whitney U-test. The statistical significance level was set at $p < 0.05$.

Results

Twenty-four patients clinically diagnosed with DCI during their course in the NIC had appropriate CBF measurements at the defined time windows both prior to the start of HHH therapy and during the therapy. Among these HHH-treated patients, 12 also had CMD data, including the time points for XeCT procedures. In the non-DCI reference group with measurements in corresponding time windows, CMD data were available for 11 patients. Clinical characteristics of these patients are presented in Table 1.

The median time point for initiation of HHH therapy was 3.1 days (IQR 1.9–4.5 days) from admission to NIC. For DCI patients, the median time for the baseline XeCT from admission was 2.0 days (IQR 1.5–4.3 days) and for the examination during HHH therapy 6.6 days (IQR 5.2–7.6 days). The median time for the reference (non-DCI) patients with XeCT in the corresponding time windows was 2.8 days (IQR 2.0–3.0 days) and 5.4 days (IQR 4.7–5.9 days; Fig. 2), respectively.

Systemic Physiological Conditions

SBP and MAP, CPP, arterial PaCO_2 , body temperature, and hematocrit at the start of the XeCT measurements at baseline and at the second time window are presented for the respective groups in Table 2 (lower). During HHH therapy, the mean SBP for the HHH-treated DCI group was increased from 152.9 mm Hg (95% CI 141.5–164.3 mm Hg) at baseline to 160.7 mm Hg (95% CI 151.6–169.9 mm Hg), but this increase was not statistically significant. In the DCI group there was a moderate decrease in hematocrit from 34.9% (95% CI 33.2%–36.6%) at baseline to 30.6% (95% CI 29.0%–32.2%; $p = 0.001$). Dobutamine and norepinephrine were used in only a few patients and at low doses; the number of patients and dose ranges are shown in Table 2. In the reference group, modest elevations of PaCO_2 and body temperature between the two measurements were noted. No significant differences were found for these parameters in the DCI group (Table 2).

FIG. 2. Median time (days) from admission to the baseline XeCT CBF measurement and to the measurement during HHH therapy for DCI patients (gray), and time to the corresponding measurements for the reference group (non-DCI patients; white). Circles and + sign indicate values exceeding 1.5 times the IQR.

CBF at Baseline

Global cortical CBF at baseline among patients subsequently diagnosed with DCI was markedly lower than for patients in the reference group: median 30.4 ml/100 g/min (IQR 25.1–33.8 ml/100 g/min) compared with 40.1 ml/100 g/min (IQR 31.5–60.1 ml/100 g/min; $p = 0.026$; Fig. 3A). There were also differences in rCBF parameters at baseline (Fig. 3B and C). Median rCBF of the worst vascular territory in the DCI group was 19.6 ml/100 g/min (IQR 12.1–26.5 ml/100 g/min) compared with 30.4 ml/100 g/min (IQR 21.4–53.2 ml/100 g/min) in the reference group ($p = 0.005$). The proportion of low-flow ROI area (local CBF < 20 ml/100 g/min) was a median of 27.7% (IQR 9.8%–39.4%) compared with 6.7% (1.7%–16.7%; $p = 0.007$) in the reference group.

Changes in Global and rCBF During HHH Therapy

The results of the CBF measurements at baseline and during HHH therapy and corresponding measurements for the reference group are presented in Table 2 and Fig. 3. For patients receiving HHH therapy, there was a significant increase in global cortical CBF from 30.4 ml/100 g/min (IQR 25.1–33.8 ml/100 g/min) to 38.4 ml/100 g/min (IQR 34.2–46.1 ml/100 g/min; $p = 0.006$; Fig. 3A). A similar pattern was seen for rCBF during HHH therapy with an increase in rCBF of the worst vascular territory from a median of 19.6 ml/100 g/min (IQR 12.1–26.5 ml/100 g/min) to 31.5 ml/100 g/min (IQR 22.1–38.5 ml/100 g/min; $p = 0.005$) and a decrease in proportion of low-flow ROI area (local CBF < 20 ml/100 g/min) from a median of 27.7% (9.8%–39.4%) to 7.2% (2.0%–23.0%; $p = 0.019$; Fig. 3B and C).

Concerning the reference (non-DCI) group, a small decrease in CBF between the two measurements was statistically nonsignificant, and the regional parameters remained at an unchanged level at the second time window.

Regional CBF in Proximity to the CMD Catheter Versus Global Cortical CBF

At the baseline measurement, the worst vascular territory was found ipsilateral to the location of the CMD catheter in 4 of the 12 DCI patients and in 4 of the 11 reference patients. Regional CBF of the ROI set in the area near the tip of the CMD catheter followed the same pattern as the

global CBF and rCBF for both DCI and reference patients (Fig. 3D). In the DCI group, rCBF CMD increased from 25.6 ml/100 g/min (IQR 22.5–35.9 ml/100 g/min) to 37.4 ml/100 g/min (IQR 30.2–46.5 ml/100 g/min; $p = 0.004$). Based on all XeCT measurements conducted in the 23 patients, there was a positive correlation between global cortical CBF and rCBF of the CMD ROI (Spearman correlation $r_s = 0.68$, $p < 0.001$; Fig. 4).

Metabolic CMD Parameters at Baseline

Data for the metabolic CMD parameters are presented in conjunction with CBF parameters in Table 2 and Fig. 3E–H. CMD lactate at baseline for patients subsequently diagnosed with DCI was 4.37 mmol/L (IQR 3.41–5.58 mmol/L) compared to 2.42 mmol/L (IQR 2.13–2.97 mmol/L; $p = 0.026$) for non-DCI patients in the reference group. The difference in CMD pyruvate between the groups at baseline did not reach statistical significance (162.0 μ mol/L [IQR 113.2–179.1 μ mol/L] vs 117.5 μ mol/L [IQR 85.7–174.1 μ mol/L]). The L/P ratio was higher in the DCI group: 26.9 (IQR 22.9–48.5) versus 20.3 (IQR 18.8 vs 26.2; $p = 0.044$). There was no significant difference in baseline CMD glucose between the groups.

Metabolic CMD Parameters During HHH Therapy in DCI Patients

During HHH therapy there was no significant change in CMD lactate from the baseline level (4.37 mmol/L [IQR 3.41–5.58 mmol/L] at baseline vs 4.78 mmol/L [IQR 3.71–5.15 mmol/L] during HHH). CMD pyruvate and the L/P ratio also stayed statistically unchanged at the same levels as in the baseline measurements (Table 2, Fig. 3F–H). Similarly, no change was noted in the CMD glucose level for the DCI group.

Metabolic CMD Parameters Over Time for the Reference Group

For the non-DCI patients in the reference group, a slight decrease was detected in CMD glucose from 2.52 mmol/L (IQR 1.27–2.87 mmol/L) at baseline to 1.77 mmol/L (IQR 0.74–2.60 mmol/L) at the day 5–8 time window ($p = 0.050$). There was also a small increase in CMD lactate from 2.42 mmol/L (IQR 2.13–2.97 mmol/L)

TABLE 2. XeCT CBF parameters and CMD data for patients subsequently diagnosed with DCI at baseline and during HHH therapy

Parameter	DCI at Baseline (n = 12)			DCI During HHH			No DCI at Baseline (n = 11)			No DCI on Days 5–8		
	Median	IQR	p <0.05	Median	IQR		Median	IQR	p <0.05	Median	IQR	
XeCT CBF parameters												
Global CBF, ml/100 g/min	30.4	25.1–33.8	0.006	38.4	34.2–46.1		40.1	31.5–60.1		38.4	29.2–46.2	
% ROI area (rCBF <20)	27.7	9.8–39.4	0.019	7.2	2.0–23.0		6.7	1.7–16.7		4.0	2.0–23.9	
% ROI area (rCBF <10)	6.8	0.0–11.7		0.0	0.0–2.4		0.0	0.0–1.7		0.0	0.0–3.5	
rCBF worst, ml/100 g/min	19.6	12.1–26.5	0.005	31.5	22.1–38.5		30.4	21.4–53.2		29.7	18.4–36.2	
rCBF CMD, ml/100 g/min	25.6	22.5–35.9	0.004	37.4	30.2–46.5		36.1	27.7–54.4		33.4	29.2–49.8	
CMD lactate, mmol/L	4.37	3.41–5.68		4.78	3.71–5.15		2.42	2.13–2.97	0.041	3.19	2.42–3.97	
CMD pyruvate, μmol/L	162.0	113.2–179.1		153.2	133.4–166.9		117.5	85.7–174.1		139.5	115.6–187.1	
CMD L/P ratio	26.9	22.9–48.5		31.6	22.4–35.7		20.3	18.8–26.2		21.6	18.6–24.7	
CMD glucose, mmol/L	1.79	1.24–2.73		1.82	0.89–3.16		2.52	1.27–2.87	0.050	1.77	0.74–2.60	
CMD glutamate, μmol/L	10.0	1.89–66.0		9.02	1.19–28.8		2.26	0.68–6.80		1.18	0.88–6.81	
Systemic Physiological Conditions												
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
SBP, mm Hg	152.9	141.5–164.3		160.7	151.6–169.9		150.0	136.2–163.7		154.1	139.8–168.3	
MAP, mm Hg	93.3	86.8–99.8		98.5	92.0–105.0		89.8	82.7–97.0		94.3	86.2–102.4	
CPP, mm Hg	81.5	75.4–87.6		84.7	78.6–90.8		76.0	68.7–83.4		82.9	74.4–91.5	
Hematocrit, %	34.9	33.2–36.6	0.001	30.6	29.0–32.2		33.4	31.3–35.5		31.6	29.6–33.5	
PaCO ₂ , mm Hg	39.9	37.7–42.1		41.7	39.4–44.1		38.1	36.2–40.1		42.6	38.5–46.7	
Body temperature, °C	37.9	37.4–38.3		38.3	38.0–38.6		37.8	37.5–38.1		38.2	37.7–38.6	
Propofol, mg/kg/hr	2.44	1.95–2.95		2.61	2.05–3.18		3.11	2.17–4.05		2.56	1.3–3.82	
	No.	Range		No.	Range		No.	Range		No.	Range	
Dobutamine, n (μg/kg/min)	0	—		2	1.8–4.5		3	1.2–10.0		2	3.5–6.2	
Norepinephrine, n (μg/kg/min)	0	—		0	—		2	0.01–0.07		2	0.05–0.05	

The reference group (non-DCI patients) had measurements at corresponding time windows. The lower part of the table shows systemic hemodynamic parameters, ventilation, sedation, and vasoactive medication at the time of XeCT measurements.

FIG. 3. Box plots (median, IQR) of CBF parameters (A–D) and cerebral microdialysis parameters (E–I) at baseline and during HHH therapy for patients diagnosed with DCI (gray) or at day 5–8 for the reference group (white). **A:** Global cortical CBF. **B:** Regional CBF of worst vascular territory. **C:** Proportion of ROI area with CBF < 20 ml/100 g/min. **D:** Regional CBF of CMD ROI. **E:** CMD glucose. **F:** CMD lactate. **G:** CMD pyruvate. **H:** CMD L/P ratio. **I:** CMD glutamate.

to 3.19 mmol/L (IQR 2.42–3.97 mmol/L; $p = 0.041$), while pyruvate and the L/P ratio stayed statistically unchanged.

Patients Categorized by CMD Energy Metabolic Patterns at the Two CBF Measurements

When the classification of three different CMD patterns (normal, mitochondrial dysfunction, or ischemia) was applied to the DCI group at baseline, there were 4 patients in mitochondrial dysfunction, 1 in ischemia, and 7 were normal (Fig. 5). At the measurement during HHH therapy, no patient showed ischemia, 8 patients were categorized with a pattern of mitochondrial dysfunction, and 4 were normal. In the reference group of non-DCI patients, all were categorized as normal both at baseline and at the second time window (Fig. 5).

Excitotoxicity: CMD Glutamate

At baseline, median CMD glutamate for the DCI group was 10.0 $\mu\text{mol/L}$ (IQR 1.89–66.0 $\mu\text{mol/L}$) compared to 2.26 $\mu\text{mol/L}$ (IQR 0.68–6.80 $\mu\text{mol/L}$) for the reference group, but the difference did not reach statistical significance ($p = 0.065$; Table 2, Fig. 3I). There was no significant change from baseline to the second measurement for either of the groups. In the DCI group, CMD glutamate

exceeding 15 $\mu\text{mol/L}$ was noted in 6 patients at baseline and in 4 during HHH, suggesting excitotoxicity, whereas only 1 patient in the reference group had CMD glutamate above this threshold.

Clinical Course and Infarcts at NIC Discharge

At discharge from the NIC, 7 (58%) of 12 patients in the DCI group and 9 (82%) of 11 patients in the reference group had a Glasgow Coma Scale (GCS) motor score of 6 (Table 1). One of the patients in the reference group died on day 11 in the NIC. Infarcts > 20 mm at follow-up CT (day 12 or later) were found in 2 patients in the DCI group (17%) and 4 patients (36%) in the reference group.

Discussion

The standardized protocol for SAH in our unit includes cautious application of HHH therapy with focus on ensuring adequate intravascular filling and keeping a moderate blood pressure target, as described in the *Methods* section. In a previously published study on the effect of HHH therapy in patients with poor-grade SAH in our unit, an increase in CBF during treatment was concluded.⁹ The intention with the present study was to investigate whether

FIG. 4. Scatterplot and regression line of global cortical CBF and rCBF at the area adjacent to the CMD catheter based on all XeCT measurements conducted in the 23 patients (DCI and reference group). There was a positive correlation between global cortical CBF and rCBF of the CMD catheter ROI area; Spearman correlation $r_s = 0.68$, $p < 0.001$.

the energy metabolic pattern, as measured by interstitial CMD, changes in concordance with the improvement in CBF during HHH therapy.

The patients who later developed DCI had markedly lower global cortical CBF at baseline compared to patients in the reference group, which is consistent with other studies.^{3,28} CBF of the worst vascular territory and the proportion of ROI area with near-ischemic flow showed corresponding differences. Regarding the CMD parameters, there was a significantly higher lactate level in the DCI group at baseline, and there was also a higher L/P ratio for this group. It appears plausible that the pathological metabolic state at baseline reflects the situation with compromised CBF in the DCI patients, as has been demonstrated in earlier studies.^{21,24} When the DCI patients were categorized by energy metabolic CMD patterns, only 1 of the DCI patients was found in ischemia at baseline and 4 in mitochondrial dysfunction, indicating that the energy metabolic derangement was moderate in the majority of these patients.

At the measurement during HHH therapy in the DCI group, there was an increase in both global cortical CBF and rCBF of the worst vascular region. There was also a marked reduction in the proportion of ROI area with near-ischemic flow. However, the CMD lactate level as well as pyruvate and the L/P ratio stayed statistically unchanged during HHH. Following clinical diagnosis of DCI and the start of HHH therapy, the proportion of patients with an energy metabolic CMD pattern of mitochondrial dysfunction increased from 4 to 8, and 4 remained in a normal CMD pattern. Previous CMD studies similarly found ischemia to be a much less common type of energy crisis than mitochondrial dysfunction in both SAH and TBI

FIG. 5. Patients categorized by three cerebral microdialysis patterns at baseline and during HHH therapy for the DCI group (gray) or at day 5–8 for the reference group (white). ISC = ischemia (L/P ratio > 30, pyruvate < 70 $\mu\text{mol/L}$); MDYS = mitochondrial dysfunction (L/P ratio > 30, pyruvate > 70 $\mu\text{mol/L}$); NORM = normal (lactate < 4 mmol/L, L/P ratio < 30).

patients.^{14,22} Our results are also consistent with a previous study on SAH patients showing no significant effect of HHH therapy on CMD glucose, lactate, or L/P ratio in DCI patients despite clinical neurological improvement.³⁰ The value of these observations is limited due to the low number of patients in our study, but suggests that the HHH therapy may have been beneficial, however with a common occurrence of disturbed energy metabolism despite improved CBF. As the mode of HHH in our standard protocol is cautious, it cannot be ruled out that more aggressive hemodynamic therapy would show different results.

Among the patients in the reference group, a small decrease in global cortical CBF at the second time window did not reach statistical significance, and the regional parameters remained unchanged. There was also a small, statistically significant increase in CMD lactate in these patients, but pyruvate and the L/P ratio were unchanged, all at a lower level compared to the DCI group. These findings are consistent with the reference group having less affected CBF and no obvious clinical signs of DCI.

Regarding excitotoxicity, an increase in CMD glutamate has been associated with neurological deterioration and ischemic changes in SAH patients.²⁹ Although the trend was a higher glutamate level in the DCI group at baseline, the range was wide and the difference between the groups did not reach statistical significance. The glutamate level stayed unchanged for both groups at the second measurement. These data support the findings of the energy metabolic patterns, but are partly in contrast to the previously mentioned CMD study in which the glutamate level decreased after HHH therapy.³⁰

No specific analysis of outcome was attempted due to the relatively small group of patients with SAH studied. To reflect the clinical course, the GCS motor score and pres-

ence of infarcts at NIC discharge were determined. The picture was somewhat ambiguous, as the reference group had a numerically higher proportion of patients with favorable GCS motor score, but fewer infarcts were detected in the DCI group.

Limitations

There are some inherent limitations in this observational study. First, there is no valid control group, as all patients with clinical signs of DCI received HHH therapy following our standard protocol. The non-DCI patients, referred to as a reference group, may have differences in the pathophysiology of cerebral hemodynamics and energy metabolism that make comparisons inconclusive. Second, the number of patients receiving HHH therapy, who also had CBF measurements in adequate time windows and had functioning CMD throughout the treatment course, was limited. The low number of patients makes generalization of our findings uncertain, and large differences are required to obtain statistical significance. A third shortcoming is from the method of CMD, reflecting the metabolic situation in a rather small region of the brain. This limits the ability of CMD to detect localized or scattered disturbances in the cerebral circulation. There was, however, a good correlation between global CBF and rCBF in the CMD region, which has also been demonstrated in previous studies.²⁶

Conclusions

The main findings of this study are that global and rCBF improved and the cerebral energy metabolic CMD parameters stayed statistically unchanged during HHH therapy in DCI patients. None of the patients developed metabolic signs of severe ischemia, but a disturbed energy metabolic pattern was a common occurrence, possibly explained by mitochondrial dysfunction despite a proposed beneficial effect from HHH on the cerebral microcirculation. Our findings emphasize the importance of hemodynamic management and multimodal monitoring in poor-grade SAH patients to optimize CBF, but also imply that other factors impairing the cerebral energy metabolism at the cellular level should be addressed in future research.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Engquist. Analysis and interpretation of data: Engquist, Hillered, Enblad, Rostami. Drafting the article: Engquist, Enblad, Rostami. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Engquist. Study supervision: Enblad, Rostami.

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