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Gastric tonometry after subarachnoid hemorrhage

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Abstract *Objective*: To evaluate splanchnic tissue perfusion, assessed by gastric tonometry, in patients with subarachnoid hemorrhage (SAH) and to study the effect of treatment, either surgical or endovascular, and the severity of initial SAH on splanchnic tissue perfusion.
Design: Prospective observational substudy, part of a randomised controlled trial of early treatment of ruptured intracranial aneurysms.
Setting: Intensive care unit (ICU) of a university hospital.
Patients: A consecutive sample of 26 patients [13 surgical (7/6 Hunt & Hess Grade I–II/H & H Gr IV–V) and 13 endovascular (3/10 H & H Gr I–II/H & H Gr IV–V)] out of 56 SAH patients randomly assigned to either endovascular or surgical treatment during the substudy period between 1 May 1995 and 31 August 1996. All patients were treated within 72 h after SAH.
Measurements and results: After treatment of a ruptured aneurysm, hemodynamics and gastric intramucosal pCO_2 were measured during the first 4 h and between 6 h and 12 h after aneurysm treatment. In the whole sample, neither the gastric intramucosal-arterial pCO_2 difference (pCO_2 gap) (1.5 ± 1.9 kPa and 1.7 ± 1.2 kPa, NS) nor gastric intramucosal pH (7.28 ± 0.12 and 7.29 ± 0.08, NS) changed during the study. There were no differences in pCO_2 gap or gastric intramucosal pH between treatment groups or Hunt & Hess grade groups during the study period.
Conclusions: Splanchnic tissue perfusion may be insufficient even though there is no systemic hemodynamic disturbance in patients after SAH. Neither the therapeutic treatment nor pre-treatment Hunt & Hess grade is associated with a specific pattern of pCO_2 gap.

Keywords Intensive care · Endovascular therapy · Splanchnic circulation · Subarachnoid hemorrhage · Surgery · Tonometry

Introduction

The initial severity of aneurysmal subarachnoid hemorrhage (SAH) determines the neurological outcome of the patients [1, 2, 3, 4]. Due to the risk of rebleeding, early treatment is preferable [2, 5, 6, 7]. Open surgical ligation of the acutely ruptured aneurysm may worsen the severity of brain injury [8, 9, 10]. In theory, endovascular treatment by Guglielmi detachable coils (GDC) [11] could be less traumatic for the brain [12].

Half of the aneurysmal SAH patients may develop extracerebral organ failures correlating with the neurological impairment, and nearly one-third of these patients may develop the systemic inflammatory response

syndrome (SIRS) [13]. Mortality in SAH patients with SIRS may be as high as 40 % [13]. Hypovolemia occurs after SAH and it may play an important role in the development of both cerebral vasospasm and extracerebral complications [14, 15]. Hypovolemia alone or associated with impaired left ventricular performance or increased sympathetic hyperactivity may predispose these patients to gut mucosal hypoperfusion. Insufficient splanchnic tissue perfusion has been regarded as one of the possible mechanisms responsible for SIRS and multiple organ failure in critically ill patients [16]. The brain injury initiates a local inflammatory response in the brain and, in addition, may contribute to a systemic inflammatory response. Interleukin (IL)-6 and -8 levels have been shown to increase both locally and in the systemic circulation in patients with SAH [17, 18, 19]. SAH is also associated with increased activity of the sympathetic nervous system; plasma concentrations of epinephrine and norepinephrine increase depending on the severity of the neurologic injury [20]. The splanchnic circulation has a rich sympathetic innervation and circulating catecholamines may provoke vasoconstriction and impair splanchnic tissue perfusion. In patients with SAH, insufficient splanchnic tissue perfusion may contribute to the development of SIRS and multiple organ failure. There is, however, a lack of data on splanchnic tissue perfusion in SAH patients.

We hypothesized that splanchnic hypoperfusion may occur after SAH depending on the severity of the injury. Between February 1995 and August 1997 we conducted a randomized study on the outcomes of treatment of aneurysmal SAH either by conventional surgical clipping or by GDC occlusion. In a sample of patients, we evaluated splanchnic tissue perfusion by gastric tonometry immediately after surgical or endovascular treatment.

Material and methods

The study was approved by the Ethics Committee of the hospital. The study included 26 patients from our previously published study in which 109 patients with subarachnoid hemorrhage were randomly assigned to either endovascular or surgical treatment [21, 22]. During this substudy period between 1 May 1995 and 31 August 1996, 56 patients were randomized for treatment. Twenty-six patients (13 surgical/13 endovascular) were included in the study and 30 patients (16 surgical/14 endovascular) were excluded because they did not tolerate the stiff gastric tonometry tube. All the patients had their aneurysms treated within 72 h after SAH. According to the study protocol, systemic hemodynamics, oxygen transport, and gastric mucosal perfusion, assessed by gastric tonometry, were measured during the first 4 h and between 6 h and 12 h after surgical or endovascular treatment. Thus, all the measurements were performed within 84 h after SAH. We analyzed the data within the whole group but also according to treatment groups (surgical/endovascular) and pretreatment clinical condition (Hunt & Hess [23] grade I–II/Hunt & Hess grade III–V).

Diagnostic angiography was followed by randomization and, if indicated, endovascular treatment was performed in the same session. Tracker-microcatheters and Dasher-guidewires (Target Therapeutics, Fremont, Calif., USA) were used for hyperselective catheterization of the aneurysmal sac. The sac was then filled with Guglielmi electrolytically detachable coils (Target Therapeutics) (Guglielmi) [21]. A standard microsurgical method was used for clipping the aneurysmal neck with a Sugita (Mizhuo Itatogyo, Tokyo, Japan) or Aesculap (Aesculap-Platz, Tuttlingen, Germany) clip [21]. All the procedures were performed under balanced anesthesia. Induction of anesthesia was performed using thiopental, fentanyl, and muscle relaxants (in one endovascular case without relaxants). Anesthesia was maintained using N_2O in five endovascular patients and in all the rest of the patients anesthesia was also supplemented by isoflurane.

All the patients in the surgical treatment group and all except one patient in the endovascular group received pre- and postoperatively intravenous treatment with phenytoin 250 mg every 8 h, betamethasone 4 mg every 6 h and nimodipine as a continuous infusion of 0.5 μg/kg per minute. H_2-receptor antagonists were not routinely used. One patient in both treatment groups received H_2-blockers during the study period. Vasoactive drugs were not given during the study period.

A pulmonary artery catheter and gastric tonometer were inserted before or immediately after treatment. Gastric intramucosal pCO_2 was measured by saline tonometer after 30–90 min of equilibration (Tonometrics, Instrumentarium, Helsinki, Finland). The patients received an intravenous infusion of 5 % glucose. None of the patients received enteral feeding. The correct position of the tonometer was confirmed by chest X-ray. The time-corrected gastric mucosal pCO_2 was obtained by multiplying the measured saline pCO_2 by the correction factors determined by the manufacturer for equilibration times of 30–90 min. The gastric intramucosal-arterial pCO_2 difference (pCO_2 gap) was calculated as gastric intramucosal pCO_2 – arterial pCO_2. The gastric intramucosal pH was calculated by a modification of the Henderson-Hasselbach equation. Blood gas analyses and pCO_2 values from tonometer were corrected for core temperature and measured by ABL 500 Blood Gas System (Radiometer A/S, Copenhagen, Denmark). Cardiac output was measured by thermodilution in triplicate using 10 ml saline at room temperature. Plasma lactate concentrations were measured enzymatically (Stat Plus 2300, Yellow Springs Instrument, Ohio, USA).

Statistics

All analyses were performed with the SPSS PC+ statistical package (9.01, SPSS, Chicago, Ill., USA). The data distribution was examined by the Kolmogorov-Smirnov test (with the Lilliefors Significance Correction) in the whole sample and separately in the subgroups. The level of significance was considered at $P < 0.1$. Mann Whitney U-test compared the differences between the groups in demographic variables. The chi-square test was used for dichotomized discrete variables. Differences in the measurements within the whole material were tested by the paired samples *t*-test or the Wilcoxon signed rank test. Statistical significance was considered at $P < 0.05$. Differences in the measurements between the subgroups were compared by the independent samples *t*-test or the Mann Whitney U-test. As each measurement was used two times for two separate comparisons, i.e., endovascular vs surgical and Hunt & Hess grade I–II vs grade III–V, the multiple comparisons were corrected with Bonferroni's adjustment [24] and the significant *P*-value in these analyses was 0.05/2 = 0.025. Significant effects of time-group interaction were located by the independent

Table 1 Demographic data of the patients both 0–4 h and 6–12 h after operation according to intention to treat and the preoperative clinical grade (Hunt & Hess scale)

		Age (± SD) Years	Gender M/F	Time from SAH to treatment (± SD) Hours	Time from operation to sample 1 (± SD) Minutes	Time from operation to sample 2 (± SD) Minutes	Ventilator treatment at the time of sample 1 *n*/(%)	Ventilator treatment at the time of sample 2 *n*/(%)	Duration of Treatment in ICU (± SD) Days
All patients	($n = 26$)	54 ± 15	13/13	32 ± 17	129 ± 70	592 ± 79	19 (73 %)	12 (46 %)	4.7 ± 3.9
Subgroups:									
Intention to treat									
Embolization	($n = 13$)	52 ± 13	7/6	28 ± 18	126 ± 66	590 ± 90	11 (85 %)	7 (54 %)	6.3 ± 4.7
Preoperative grade									
H&H Gr I–II	($n = 3$)	43 ± 5	2/1	44 ± 30[a]	123 ± 75	595 ± 80	2 (67 %)	1 (33 %)	3.9 ± 3.4
H&H Gr III–V	($n = 10$)	55 ± 12	5/5	23 ± 11	127 ± 67	588 ± 96	9 (90 %)	6 (60 %)	7.0 ± 4.9
Surgery	($n = 13$)	53 ± 18	6/7	37 ± 16	132 ± 77	594 ± 71	8 (62 %)	5 (39 %)	3.0 ± 2.1
Preoperative grade									
H&H Gr I–II	($n = 7$)	48 ± 21	3/4	41 ± 18[a]	117 ± 86	602 ± 80	3 (43 %)	1 (14 %)	2.0 ± 0.4
H&H Gr III–V	($n = 6$)	59 ± 13	3/3	32 ± 12	150 ± 67	584 ± 65	5 (83 %)	4 (67 %)	4.1 ± 2.8

[a] $P < 0.05$. Patients in preoperative H & H Gr I–II were treated later than patients in preoperative H & H Gr III–IV

samples *t*-test or the Mann Whitney U-test after calculating new test-variables representing the differences between the first and second samples. According to Bonferroni's adjustment, the significant *P*-value in these analyses was also 0.05/2 = 0.025. All results are presented as mean ± SD.

Results

Demographic data

The distribution of the patients according to their age and gender was comparable in both treatment groups (Table 1). The patients in poor condition (pretreatment Hunt & Hess grade III–V) were older than the patients in good condition (pretreatment Hunt & Hess grade I–II) ($P = 0.126$). The patients in poor condition were treated sooner after SAH (26 ± 12 vs 42 ± 21 h; $P = 0.043$) (Table 1). In the endovascular group, in the ICU four patients each developed one extracerebral complication: sepsis, multiple organ failure, pneumonia, and renal failure. In the surgical group, we observed pulmonary edema in one patient and septic urinary infection in another complicated recovery.

Tonometric data

In the grouped data, the mean gastric intramucosal pH did not change between the first and second measurement periods, 7.28 ± 0.12 and 7.29 ± 0.08, respectively (Table 2). The pCO_2 gap also remained stable during the study period, 1.5 ± 1.9 kPa and 1.7 ± 1.2 kPa, respectively (Table 2). Gastric intramucosal pH did not differ either between Hunt & Hess grades I–II and III–V or between surgically and endovascularly treated groups (Table 2). No statistically significant difference was found in pCO_2 gap between the pretreatment Hunt & Hess grade groups (Gr I–II 1.2 ± 2.6 kPa vs 1.8 ± 0.7 kPa, Gr III–V 1.7 ± 1.5 kPa vs 1.7 ± 1.4 kPa), and the different treatment groups (endovascular 2.2 ± 2.5 kPa vs 1.9 ± 1.3 kPa, surgical 0.8 ± 0.5 kPa vs 1.5 ± 1 kPa) (Table 2). Individual changes in pCO_2 gap are shown in Fig. 1 and Fig. 2.

Hemodynamic and oxygen transport data

In the grouped data, hemodynamic variables remained stable during the study but the plasma hemoglobin concentration decreased ($P < 0.001$) (Table 3). Only for lactate was there a statistically significant time and treatment group interaction ($P = 0.012$) as well as a time and Hunt & Hess grade interaction ($P = 0.020$). However, the changes in hemoglobin and lactate concentrations were within the normal range. At the time of the first measurement, the Hunt & Hess grade I–II patients had lower arterial blood pHs (aBpH) than the Hunt & Hess grade III–V patients ($P = 0.013$) (Table 2). At the time of second measurement, the surgical patients had lower SvO_2 values than the endovascular patients ($P = 0.017$) (Table 3).

Discussion

Little is known about splanchnic tissue perfusion in neurological or neurosurgical patients. This is the first study to evaluate splanchnic tissue perfusion by gastric tonometry in patients after SAH. Our results demonstrate that splanchnic tissue perfusion, assessed by gas-

Table 2 Arterial pH, PCO2, pHi, and PCO2 gap according to intention to treat and the preoperative clinical grade (Hunt & Hess scale)

		apH		$aPCO_2$ kPa		pHi		pCO_2 gap[a] kPa	
		0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h
All patients	(n = 26)	7.39 ± 0.07	7.42 ± 0.04	4.7 ± 1.0	4.6 ± 0.7	7.28 ± 0.12	7.29 ± 0.08	1.5 ± 1.9	1.7 ± 1.2
Subgroups:									
Preoperative grade									
H&H Gr I–II	(n = 10)	7.36 ± 0.07[b]	7.42 ± 0.04	5.3 ± 1.1	4.9 ± 0.6	7.27 ± 0.12	7.29 ± 0.04	1.2 ± 2.6	1.8 ± 0.7
H&H Gr III–V	(n = 16)	7.41 ± 0.07	7.41 ± 0.05	4.3 ± 0.6	4.4 ± 0.6	7.28 ± 0.13	7.29 ± 0.10	1.7 ± 1.5	1.7 ± 1.4
Intention to treat									
Embolization	(n = 13)	7.41 ± 0.08	7.41 ± 0.05	4.4 ± 0.8	4.4 ± 0.6	7.26 ± 0.16	7.27 ± 0.08	2.2 ± 2.5	1.9 ± 1.3
Surgery	(n = 13)	7.37 ± 0.05	7.42 ± 0.03	5.0 ± 1.1	4.7 ± 0.7	7.29 ± 0.07	7.31 ± 0.07	0.8 ± 0.5	1.5 ± 1.0

[a] pCO_2 gap is the difference between intramucosal and arterial pCO_2
[b] $P < 0.025$ between the Hunt & Hess grade I–II group and the Hunt & Hess grade III–V group at the time of the 0–4 h measurement

tric tonometry, may deteriorate after acute SAH even though there is a hyperdynamic systemic circulation. Our results support the results of the study by Venkatesh in ten severe head trauma patients [25]. In their study, low intramucosal pH (< 7.30) was observed during the few first days in nine of ten patients and mean pCO_2 gap was 2.2 kPa. The limit for a normal pCO_2 gap has been regarded as 1.2 kPa, [26] but even values as high as 3.2 kPa have been used as the normal limit for the pCO_2 gap in healthy volunteers [27]. Thus, no strict limit for a normal pCO_2 gap can be set. However, 22 of our 26 patients had a pCO_2 gap higher than 1.2 kPa and three of them had a gap higher than 3.2 kPa during the study period, which suggests that splanchnic tissue perfusion, as assessed by gastric tonometry, may deteriorate after SAH. In one of these three patients, a perforation of the aneurysm complicated the treatment. Another patient developed postoperative pneumonia but in the third patient recovery was uncomplicated. Although plasma levels of norepinephrine or epinephrine correlate with the severity of SAH, [28, 29, 30] we found no correlation between the pCO_2 gap and the severity of hemorrhage. This argues against our hypothesis that a more severe injury associated with higher level of circulating catecholamines would contribute to poorer splanchnic mucosal perfusion. However, the results are in accordance with the study by Venkatesh. They found no correlation between the development of mucosal ischemia and the decrease in cerebral perfusion [25]. However, the limitation of our study is the short data collection time period compared with the study of Venkatesh and, there-

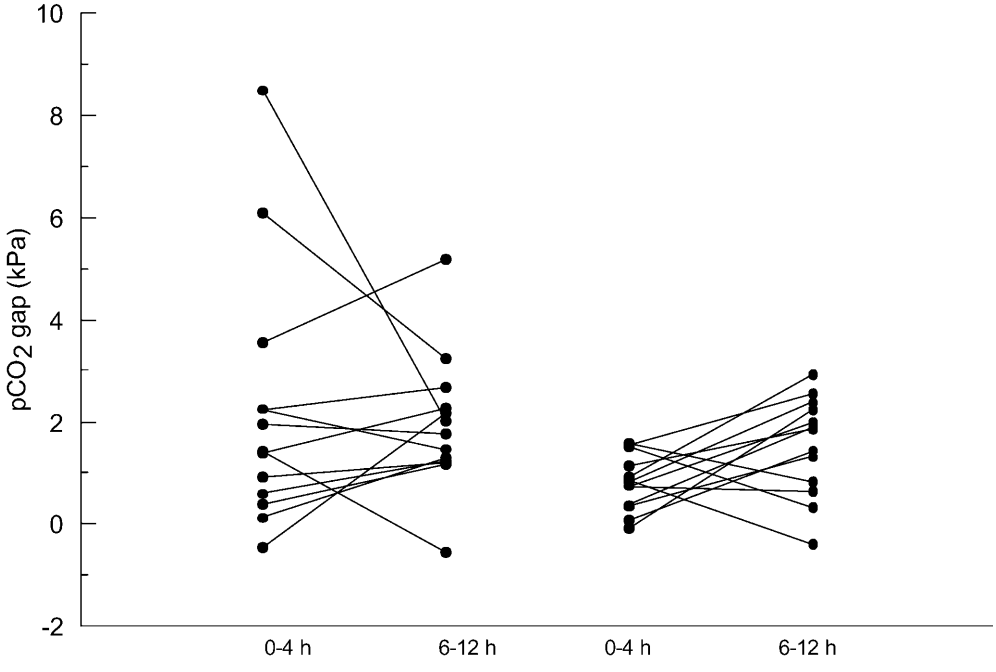

Fig. 1 Individual changes in the difference between intramucosal and arterial pCO_2 (pCO_2 gap) within 4 h and 6–12 h after aneurysm treatment subdivided according to the treatment groups

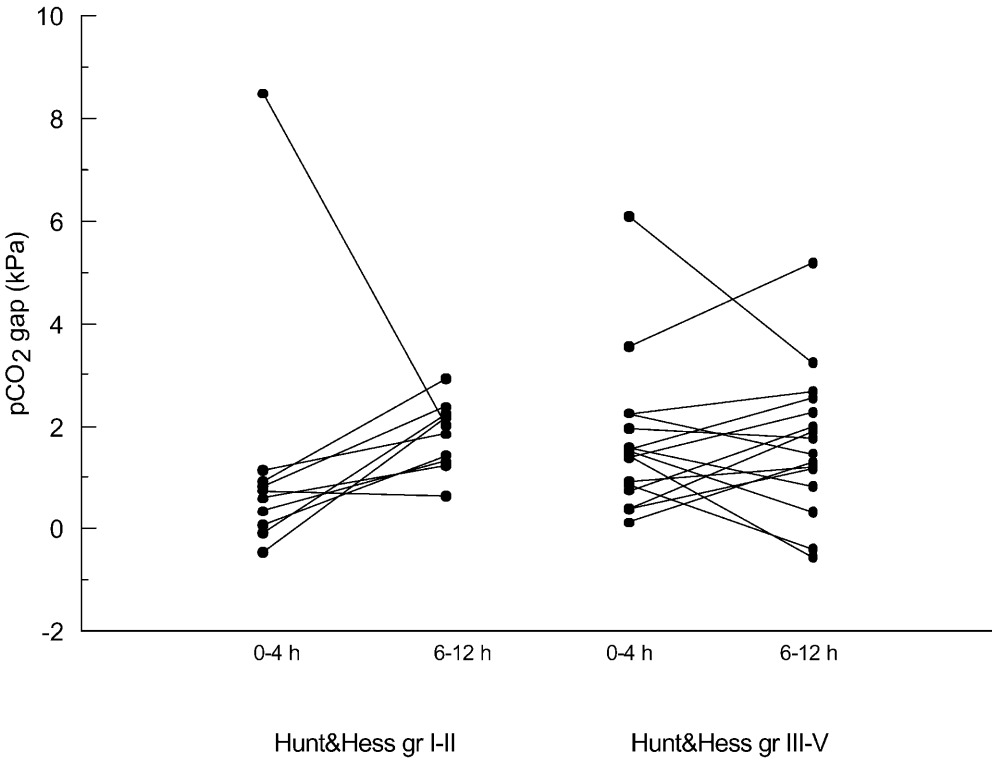

Fig. 2 Individual changes in the difference between intramucosal and arterial pCO_2 (pCO_2 gap) within 4 h and 6–12 h after aneurysm treatment subdivided according to Hunt & Hess grades

fore, the interpretation and comparison of the results must be cautious.

Why does splanchnic perfusion deteriorate in patients with SAH? First, hypovolemia is common in SAH patients [14] and in acute hypovolemia, splanchnic blood volume and flow may be markedly reduced in order to maintain the perfusion to the heart and the brain [31]. In our study, there were no signs of hypovolemia as assessed by clinical evaluation and invasive hemodynamic variables. In contrast, most of our patients had a hyperdynamic cardiovascular response. Second, concentrations of circulating catecholamines, epinephrine, and norepinephrine have been shown to increase after SAH and to be related to the clinical condition of the patients [28, 29, 30]. The activation of the sympathetic nervous system is often responsible for cardiologic complications in patients with SAH [32]. Similarly, circulating catecholamines may cause vasoconstriction in the splanchnic area and lead to deterioration of splanchnic tissue perfusion. Catecholamines may redistribute blood flow both in the splanchnic region and in the wall of the gut [33]. Third, increased levels of cytokines may have an effect on the splanchnic circulation in neurotrauma [25]. Despite the lack of major tissue damage, the metabolic response to SAH resembles the response to moderate or major trauma [34, 35]. The source of hypermetabolism after SAH is unclear. The visceral region is one possible origin for the hypermetabolism and a mismatch between oxygen delivery and consumption in the splanchnic region may contribute to the increased pCO_2 gap in patients after SAH.

The diagnostic value of gastric tonometry to detect mucosal perfusion disturbances has been challenged. In theory, a reduction in mucosal perfusion could lead to the accumulation of mucosal CO_2 after a reduced washout and later as a result of anaerobic metabolism [36]. However, the use of the method has revealed both methodological and physiological problems. Blood gas analyzers may underestimate saline pCO_2 by anything between 5–50 %, [37, 38], the fluid used in the balloon has effect on pCO_2 value [39], and any delay in analyzing saline sample may decrease saline pCO_2 [40]. Generation of CO_2 from the buffering of gastric acid by bicarbonate may cause erroneously high pCO_2 values. In healthy volunteers, H_2-antagonists have been demonstrated to reduce the generation of intraluminal CO_2 and to improve the reproducibility of pHi measurements [41, 42]. We did not use routinely H_2-antagonists due to two reasons. First, the use of H_2-antagonists has not been shown to have any effect on gastric pCO_2 or intrapatient variability in critically ill patients [43]. Second, H_2-antagonists may disturb splanchnic perfusion [44] or contribute to the development of pneumonia in critically ill patients [45]. We did not measure gastric juice pH, which could have helped to distinguish intraluminal CO_2 production by buffering of gastric acid from mucosal production of

Table 3 Hemodynamics and oxygen transport according to intention to treat and the preoperative clinical grade (Hunt & Hess scale)

		HR (± SD) Beats/min		MAP (± SD) mmHg		CI (± SD) l·min·m^2		PCWP (± SD) mmHg		Hb (± SD) g/l		Lakt (± SD) mmol/l		SvO_2 %	
		0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h	0–4 h	6–12 h
All patients	(n = 26)	74 ± 15	74 ± 12	87 ± 20	87 ± 11	3.8 ± 1.1	4.0 ± 0.9	11 ± 4	11 ± 3	125 ± 17	119 ± 16[a]	1.8 ± 0.8	1.7 ± 1.0	75 ± 5	76 ± 4
Subgroups:															
Preoperative grade															
H&H Gr I–II	(n = 10)	73 ± 17	73 ± 9	88 ± 19	93 ± 12	4.3 ± 1.5	4.4 ± 1.2	12 ± 4	12 ± 2	128 ± 14	122 ± 11	2.1 ± 0.6[c]	1.6 ± 0.5	76 ± 5	77 ± 5
H&H Gr III–V	(n = 16)	74 ± 14	75 ± 13	87 ± 21	84 ± 10	3.5 ± 0.7	3.8 ± 0.6	10 ± 4	11 ± 3	123 ± 19	118 ± 19	1.6 ± 0.8	1.8 ± 1.2	74 ± 5	75 ± 3
Intention to treat															
Embolization	(n = 13)	77 ± 12	78 ± 11	89 ± 22	86 ± 9	3.7 ± 1.1	4.1 ± 0.6	9 ± 4	11 ± 3	125 ± 21	119 ± 20	1.5 ± 0.7[d]	1.8 ± 1.2	76 ± 6	78 ± 3[b]
Surgery	(n = 13)	70 ± 17	70 ± 11	86 ± 18	89 ± 14	3.9 ± 1.2	4.0 ± 1.2	12 ± 4	12 ± 3	124 ± 13	119 ± 12	2.1 ± 0.7	1.7 ± 0.6	74 ± 5	74 ± 4

[a] $P < 0.025$ within group comparison between 0–4 h and 6–12 h measurements
[b] $P < 0.025$ between the surgical group and the endovascular group comparison at the time of the 6–12 h measurement
[c] $P < 0.025$ time and treatment group interaction
[d] $P < 0.025$ time and Hunt & Hess grade interaction

CO_2. Therefore, we cannot exclude the possibility that in some patients, the increased pCO_2 gap may due to the buffering of gastric acid by bicarbonate. Enteral feeding may disturb the evaluation of gastric perfusion and it has been recommended to use gastric tonometry in the fasting state [46]. Our patients did not receive enteral feeding during the study period. Even with these limitations, it is our view that it is possible to evaluate the relationship between gastric mucosal CO_2 production and blood flow by gastric tonometry.

Medical complications after aneurysmal SAH may significantly contribute to the overall mortality rate. The mortality rate from medical complications was 23 % in a multicenter co-operative study [47]. In our study, 23 % of the patients had extracerebral complications during their ICU stay. The number of patients in our study was small. Therefore, it is difficult to compare the type and rate of complications in this study with the complications in other related studies. In addition, the time period of our study was short, but the aim of this study was to evaluate the early response of SAH on splanchnic tissue perfusion. The results suggest that splanchnic tissue perfusion, as assessed by gastric tonometry, may be insufficient after SAH. It is apparent that treatment, either surgical or endovascular, does not affect splanchnic tissue perfusion, assessed by gastric tonometry. Furthermore, the severity of initial SAH does not modify the pCO_2 gap. The clinical relevance of the increased pCO_2 gap is unclear in SAH patients and further studies are needed to evaluate splanchnic tissue perfusion and its relation to morbidity and mortality in neurosurgical patients.

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