Brain Tissue Oxygenation Guided Therapy and Outcome in Non-Traumatic Subarachnoid Hemorrhage

Elisa GOUVEA BOGOSSIAN (elisagobog@gmail.com)
Université Libre de Bruxelles
Daniela DIAFERIA
Université Libre de Bruxelles
Narcisse NDIEUGNOU DJANGANG
Université Libre de Bruxelles
Marco MENOZZI
Université Libre de Bruxelles
Jean-Louis VINCENT
Université Libre de Bruxelles
Marta TALAMONTI
Université Libre de Bruxelles
Olivier DEWITTE
Université Libre de Bruxelles
Lorenzo PELUSO
Université Libre de Bruxelles
Sami BARRIT
Université Libre de Bruxelles
Mejdeddine AL BARAJRAJI
Université Libre de Bruxelles
Joachim ANDRE
Université Libre de Bruxelles
Sophie SCHUIND
Université Libre de Bruxelles
Jacques CRETEUR
Université Libre de Bruxelles
Fabio Silvio TACCONE
Université Libre de Bruxelles

Research Article

Keywords: brain tissue oxygenation, cerebral hypoxia, mortality, neurological outcome, multimodal monitoring, non traumatic subarachnoid hemorrahge

Posted Date: February 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-228515/v1

Version of Record: A version of this preprint was published at Scientific Reports on August 10th, 2021. See the published version at https://doi.org/10.1038/s41598-021-95602-6.

Abstract

Background

Brain hypoxia can occur after spontaneous subarachnoid hemorrhage (SAH), even when levels of intracranial pressure (ICP) remain normal. Brain tissue oxygenation (PbtO2) can be measured as a part of a neurological multimodal neuromonitoring Low PbtO2 has been associated with poor neurologic recovery. There is scarce data on the impact of $PbtO_2$ guided-therapy on patients' outcome.

Methods

This single-center cohort study (June 2014-March 2020) included all patients admitted to the ICU after SAH who required multimodal monitoring. Patients with imminent brain death were excluded. Our primary goal was to assess the impact of $PbtO_2$-guided therapy on neurological outcome. Secondary outcome included the association of brain hypoxia with outcome.

Results

Of the 163 patients that underwent ICP monitoring, 62 were monitored with $PbtO_2$ and 54 (87%) had at least one episode of brain hypoxia. In patients that required treatment based on neuromonitoring strategies, $PbtO_2$-guided therapy (OR 0.33 [CI 95% 0.12–0.90]) compared to ICP-guided therapy had a protective effect on neurological outcome at 6 months. Brain hypoxia was associated with unfavorable neurological (OR 4.51 [95% CI 1.17–17.45]).

Conclusions

In this cohort of SAH patients, $PbtO_2$-guided therapy when compared to ICP guided therapy may be associated with improved long-term neurological outcome.

Introduction

Spontaneous SAH (SAH) is a life-threatening disease that can cause severe disabilities in the survivors.[1–3] Immediately after aneurysm rupture, an acute increase in intracranial pressure (ICP), together with a decrease in cerebral perfusion, can lead to brain ischemia.[4] This phenomenon is associated with endothelial damage, excitotoxicity and neuroinflammation, all resulting in neuronal death.[5,7] All these processes, that are identified as "early brain injury", can contribute to the further increase in ICP that, if uncontrolled, will lead to severe cerebral injury and brain death.[6–8]

As such, ICP monitoring has been recommended, with the aim to early detect ICP elevation and potentially reduce early mortality.[3,9,10] However, tissue hypoxia can occur even when ICP remains within normal values,[11–13] so that ICP monitoring alone may not be sufficient to minimize cerebral ischemia in these patients. Adding brain tissue oxygenation ($PbtO_2$) monitoring in a multimodal approach (MMM) to detect cerebral hypoxia and initiate early neuroprotective intervention may improve patients' outcome.[14–16] Moreover, in a later phase of SAH, up to 30% of patients can develop delayed cerebral ischemia (DCI),[17] which is the most important determinant cause of poor outcome in SAH.[18–20] Early recognition of DCI is essential for timely interventions to minimize brain damage. As clinical examination is often unreliable in these patients (i.e. persistent poor clinical condition since admission or use of sedative drugs associated with limited clinical manifestations), $PbtO_2$ monitoring could help detect and treat brain hypoxia due to DCI.[21,22]

$PbtO_2$ monitoring has been extensively studied in traumatic brain injury (TBI) patients, where brain hypoxia is associated with poor neurologic outcome and high mortality rates.[13,23–25] Moreover, some studies using $PbtO_2$ guided-therapy have shown an improved neurological outcome when compared to ICP-guided therapy in these patients.[26–28] In SAH patients, low $PbtO_2$ values have also been associated with adverse neurologic events, such as metabolic distress, cerebral vasospasm and DCI, as well as with poor neurologic outcome.[22,29,30] However, whether $PbtO_2$-guided therapy improve patients' outcome after SAH is still a matter of debate.

To assess this issue, the aim of this study was to investigate the impact of $PbtO_2$ guided-therapy on the outcome of SAH patients. Our hypothesis was that $PbtO_2$ guided-therapy would allow improved neurological outcome via an early diagnosis and treatment of secondary brain injuries.

Methods

Study design

We reviewed our cohort of patients with spontaneous SAH treated from June 2014 until March 2020 in our Department of Intensive Care. This study was approved by the Erasme Hospital (Université Libre de Bruxelles) ethics committee (P2019/649) on May 23rd 2019, that waived the need for informed consent. All methods were carried out in accordance with relevant scientific and ethical guidelines and regulations.

All adult (> 18 years) patients admitted with SAH were eligible, provided that they needed an ICP monitoring within the first 48 hours after admission. The sole exclusion criterion was imminent death in the first 48 hours from admission, without any specific therapies and leading to early limitation of life-sustaining therapies. ICP monitoring was inserted in patients with an initial GCS < 9 or with clinical deterioration and hydrocephalus on cerebral CT-scan. The decision to add a $PbtO_2$ monitoring was mainly driven by the availability of the monitoring device (i.e. one device in 2014, then three devices since November 2017).

Patient management and definitions

A detailed account of the management of SAH patients in our department is published elsewhere.[31] Both ICP and $PbtO_2$ were measured in real-time and collected prospectively. Intracranial hypertension was defined by the observation of at least one ICP value above 20 mmHg for at least 5 min at any time. Brain tissue hypoxia was defined by a $PbtO_2$ below 20 mmHg, and severe brain hypoxia by a value less than 10 mmHg.[22] We defined the "burden of hypoxia" as the area under the curve ($PbtO_2$ x time, expressed as mmHg*hour) below 20 and 10 mmHg of $PbtO_2$, respectively. ICP-guided therapy was considered as all specific therapeutic interventions (i.e. increased sedation, osmotic therapy, hyperventilation, high-dose barbiturates, decompressive craniectomy) aiming to achieve an ICP < 20 mmHg. $PbtO_2$-guided therapy was considered as all specific therapeutic interventions (i.e. induced hypertension, changes in $PaCO_2$, red blood cells transfusions, cerebral arteriography with chemical angioplasty) aiming to achieve a $PbtO_2$ > 20 mmHg (Supplemental Fig. 1).

Data collection

We recorded demographic data, such as age, gender and presence of comorbidities. Clinical severity scores on admission, such as the Sequential Organ Failure Assessment (SOFA)[32] and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores, were computed.[33] Neurologic assessment scales and imaging scale on admission, such as the World Federation of Neurological Surgeons (WFNS) scale,[34] the Glasgow Coma Scale (GCS) [35] and the modified Fisher grading scale,[36] were reported for all patients. Patients with WFNS 4 or 5 on admission were defined as "poor grade"; patients with modified Fisher scale 3 or 4 on admission were defined as "high risk". We also recorded the type of intervention to secure the aneurysm (i.e. endovascular vs. surgical treatment), the various interventions that the patients received during the ICU stay (i.e. mechanical ventilation, vasopressor and inotropic support and renal replacement therapy) and the development of complications, including seizures, re-bleeding, cerebral vasospasm and DCI. We also recorded the specific treatments used to treat intracranial hypertension and/or tissue hypoxia. We recorded hospital mortality, the Glasgow Outcome Scale (GOS) [37] at 6 months and the occurrence of unfavorable neurological outcome (UO), as defined by a GOS at 6 months of 1–3, using medical reports from follow-up visits.

Study outcomes

We assessed the impact of ICP/$PbtO_2$-guided therapy on neurological outcome in SAH patients. In particular, a subgroup analysis including only patients receiving therapies driven by neuromonitoring (ICP-guided vs. ICP/$PbtO_2$-guided) was performed. Secondary outcomes included: a) the impact of ICP/$PbtO_2$ guided therapy on hospital mortality; c) the association of tissue hypoxia (i.e. < 20mmHg) and severe tissue hypoxia (i.e. < 10 mmHg) with neurological outcome and hospital mortality.

Statistical analysis

Descriptive statistics were computed for all variables. Numeric variables were described either as median and interquartile intervals 25% – 75% or mean and standard deviation. Categorical variables were described as proportions. We assessed the distribution pattern of each variable using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using t Student test and asymmetrically distributed variables were compared using Mann-Whitney test. Categorical variables were analyzed using chi square or Fisher's exact test, as appropriate. We performed a binary logistic regression to assess the association of ICP/$PbtO_2$ -guided therapy with UO, adjusted by clinically relevant confounders. Similarly, we conducted a Cox regression to evaluate the association of ICP/$PbtO_2$ -guided therapy and hospital mortality, adjusted for confounders. In the subgroup of patients that received interventions based on MMM, we performed a logistic regression to assess a possible association between ICP/PbtO2 guided therapy compared to ICP guided therapy and neurological outcome in 6 months. In the $PbtO_2$ monitored group we also conducted a multivariable analysis to assess the possible association of brain hypoxia and severe brain hypoxia adjusted for $PbtO_2$ guided therapy and intracranial hypertension with unfavorable neurological outcome and mortality. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed for all variables in all multivariable models. The independence of errors, presence of multicollinearity and the presence of influential outlier assumptions were checked and none of them were violated. We used a linear mixed equation model using the restricted maximum likelihood approach to express the distribution of $PbtO_2$ levels over time according to survival status at hospital discharge and neurological status at 6 months. All statistical analysis was done using the program SPSS 27.0 for MacIntosh. A p value < 0.05 was considered significant.

Results

Study population

Of a total of 322 patients admitted for non-traumatic spontaneous SAH, 168 were monitored with ICP monitoring. Five patients died within 48 hours, so that 163 patients were included in the analysis: 97 monitored with ICP only and 66 with ICP and $PbtO_2$ (ICP/$PbtO_2$ group). However, 4 patients had malfunctioning/misplaced $PbtO_2$ catheters and were eventually analyzed into the ICP group (Fig. 1). In the ICP only monitored group, 43/101 (43%) patients received ICP-guided therapy; in the ICP/$PbtO_2$ group, 54/62 (87%) received ICP/$PbtO_2$-guided therapy, of which 22 received treatment triggered only by $PbtO_2$. Also, in the ICP/$PbtO_2$ group, 5/62 (8%) patients received ICP but not $PbtO_2$-guided therapy.

Patients were predominantly female (97/163, 60%) and had a mean age of 55 (± 13) years (Table 1); the median GCS on admission was 6 (3–12). An aneurysm was identified in 143/163 (88%) patients. The most common comorbidity was arterial hypertension (80/163, 49%) and hydrocephalus was the most common neurological complication (111/163, 68%). DCI occurred in 59 (36%) patients and intracranial hypertension in 95 (58%) patients during ICU stay. Sixty-eight patients (42%) died at hospital discharge and 111 (68%) patients had UO at 6 months.

Table 1
Characteristics of the studied population, according to the type of neuro-monitoring. Data are presented as count (%), mean ± SD or median (IQRs).

	All patients (N = 163)	ICP (N = 101)	ICP/$PbtO_2$ (N = 62)	p -value
On Admission				
Age, mean (± SD)	55 (± 13)	55 (± 13)	54 (± 12)	0.42
Male gender, n (%)	66 (41)	41 (41)	25 (40)	0.99
APACHE score, median (IQR)	18 (13–21)	18 (13–21)	19 (13–22)	0.80
SOFA score, median (IQR)	7 (4–10)	7 (4–9)	8 (4–10)	0.42
GCS, median (IQR)	6 (3–12)	6 (3–11)	4 (3–13)	0.51
WFNS 4–5, n (%)	126 (77)	80 (79)	46 (74)	0.56
mFisher scale 3 or 4 points, n (%)	154 (95)	99 (98)	55 (89)	0.03
Intraparenchymal hematoma, n (%)	60 (37)	30 (30)	30 (48)	0.02
Comorbidities				
HAS, n (%)	80 (49)	55 (55)	25 (40)	0.11
DM, n (%)	18 (11)	13 (13)	5 (8)	0.44
Heart disease, n (%)	18 (11)	13 (13)	5 (8)	0.44
Previous neuro disease, n (%)	17 (10)	14 (14)	3 (5)	0.11
CKD, n (%)	4 (3)	3 (3)	1 (2)	0.99
Asthma /COPD, n (%)	17 (10)	11 (11)	6 (10)	0.99
Immunosuppression, n (%)	9 (6)	7 (7)	2 (3)	0.49
Cancer, n(%)	11 (7)	9 (9)	2 (3)	0.21
Cirrhosis, n(%)	7 (4)	5 (5)	2 (3)	0.71
Support therapies during ICU stay				
Vasopressor, n(%)	124 (76)	66 (65)	58 (94)	0.001
Inotropic, n(%)	45 (28)	9 (9)	36 (58)	0.001

N = number; IQR: interquartile range; APACHE : acute physiology and chronic health evaluation; SOFA : sequential organ failure assessment; GCS: Glasgow coma scale; WFNS: world federation of neurological surgeons; COPD: chronic obstructive pulmonary disease; RRT: renal replacement therapy; ECMO: extra-corporeal membrane oxygenation. $PbtO_2$: brain tissue oxygenation; DCI: delayed cerebral ischemia; ICU: intensive care unit; LOS: length of stay; GOS: Glasgow outcome scale.

	All patients (N = 163)	ICP (N = 101)	ICP/$PbtO_2$ (N = 62)	p -value
Mechanical ventilation, n(%)	146 (90)	86 (85)	60 (97)	0.02
RRT, n (%)	1 (1)	1(1)	0	0.99
ECMO, n (%)	3 (2)	2 (2)	1 (2)	0.99
Treatments				
Surgical clipping, n (%)	33 (20)	15 (15)	18 (29)	0.04
Endovascular coiling, n (%)	102 (63)	62 (61)	40 (65)	0.74
Nimodipine (prophylaxis), n (%)	141 (87)	89 (88)	52 (84)	0.48
Osmotic therapy, n (%)	74 (45)	43 (43)	31 (50)	0.42
Induced Hypertension, n (%)	97 (60)	53 (53)	44 (71)	0.001
Barbituric coma, n (%)	34 (21)	14 (14)	20 (32)	0.009
Induced hypothermia, n (%)	30 (18)	9 (9)	21 (34)	0.001
Decompressive craniectomy, n (%)	15 (9)	6 (6)	9 (15)	0.09
Intra-arterial nimodipine, n (%)	53 (33)	20 (20)	33 (53)	0.001
Angioplasty, n (%)	23 (14)	12 (12)	11 (18)	0.36
ICP/PbtO2 Guided-therapy				0.001
No therapy	61 (37)	58 (57)	3 (5)	< 0.05
ICP/PbtO2 guided therapy	54 (33)	0	54 (87)	< 0.05
ICP only guided therapy	48 (29)	43 (43)	5 (8)	< 0.05
Neurological complications				
Seizures, n (%)	59 (36)	43 (43)	16 (26)	0.04
Rebleeding, n (%)	15 (9)	5 (5)	10 (16)	0.03
Hydrocephalus, n (%)	111 (68)	82 (81)	29 (47)	0.001
DCI, n (%)	59 (36)	30 (30)	29 (47)	0.03
Intracranial hypertension, n (%)	95 (58)	55 (55)	40 (65)	0.25

N = number; IQR: interquartile range; APACHE : acute physiology and chronic health evaluation; SOFA : sequential organ failure assessment; GCS: Glasgow coma scale; WFNS: world federation of neurological surgeons; COPD: chronic obstructive pulmonary disease; RRT: renal replacement therapy; ECMO: extra-corporeal membrane oxygenation. $PbtO_2$: brain tissue oxygenation; DCI: delayed cerebral ischemia; ICU: intensive care unit; LOS: length of stay; GOS: Glasgow outcome scale.

	All patients (N = 163)	ICP (N = 101)	ICP/$PbtO_2$ (N = 62)	p -value
Outcomes				
ICU LOS- days (IQR)	16 (10–22)	15 (10–21)	18 (9–26)	0.20
Hospital LOS- days (IQR)	27 (13–52)	28 (13–49)	25 (10–54)	0.78
GOS -points, median (IQR)	3 (1–4)	3 (1–5)	2 (1–4)	0.15
Unfavorable outcome, n (%)*	111 (68)	60 (59)	38 (61)	0.87
ICU death	64 (39)	34 (34)	30 (48)	0.07
Hospital death	68 (42)	38 (38)	30 (48)	0.19

N = number; IQR: interquartile range; APACHE : acute physiology and chronic health evaluation; SOFA : sequential organ failure assessment; GCS: Glasgow coma scale; WFNS: world federation of neurological surgeons; COPD: chronic obstructive pulmonary disease; RRT: renal replacement therapy; ECMO: extra-corporeal membrane oxygenation. $PbtO_2$: brain tissue oxygenation; DCI: delayed cerebral ischemia; ICU: intensive care unit; LOS: length of stay; GOS: Glasgow outcome scale.

ICP and ICP/$PbtO_2$ monitoring

The characteristics of the two groups are shown in Table 1. Patients in the ICP/$PbtO_2$ group underwent more frequently vasopressors or inotropic therapy and required more frequently invasive mechanical ventilation. Although the most used modality of treatment of the culprit aneurysm was endovascular coiling in the whole cohort, patients in the ICP/$PbtO_2$ group presented more frequently with intraparenchymal hematoma and underwent more frequently surgical clipping than patients in the ICP group. The patients in the ICP/$PbtO_2$ group developed more neurological complications such as re-bleeding and DCI than the other patients. Both ICU and hospital mortality were numerically higher, although not significantly different, in the ICP/$PbtO_2$ group, while UO was similar in both groups.

Of the 62 patients in the ICP/$PbtO_2$ group, brain hypoxia occurred in 54/62 (87%) patients and severe brain tissue hypoxia occurred in 39/62 (63%) patients. The overall burden of brain tissue hypoxia was 316.48 (102.32-560.89) mmHg*h. The burden of severe brain hypoxia was 36.88 (10.25-158.75) mmHg*h.

Unfavorable neurological outcome and $PbtO_2$ guided therapy

Patients with UO had higher severity scores on admission, received more frequently vasopressors and mechanical ventilation, were more often treated with surgical clipping and less frequently with prophylactic nimodipine. They also developed more complications (re-bleeding, intracranial hypertension and DCI; Supplemental Table S1). However, the proportion of patients receiving ICP/$PbtO_2$ guided therapy

(34/98, 35% vs. 20/65, 31%, p = 0.62) was similar between the two groups. In the multivariable analysis (Table 2) adjusted for age, poor grade on admission, the development of intracranial hypertension, DCI, presence of intraparenchymal hematoma, endovascular treatment, nimodipine prophylaxis, combined ICP/$PbtO_2$-guided therapy (0.55 [0.20–1.46]) was not independently associated with UO.

Table 2
Logistic regression analysis to identify variables independently associated with 6-month unfavorable neurologic outcome. Data are reported as odds ratio (OR) and 95 % confidence intervals (CIs).

	Univariable analysis	**Multivariable analysis**
	OR (95% CI)	**OR (95% CI)**
Age	1.02 (1.00-1.05)	1.06 (1.02–1.01)
Poor Grade (WFNS 4–5)	2.45 (1.16–5.16)	2.00 (0.77–5.23)
Intracranial hypertension	8.36 (4.09–17.09)	9.19 (3.87–21.82)
DCI	3.09 (1.52–6.31)	7.66 (2.71–21.69)
Endovascular (coiling) treatment	0.62 (0.32–1.20)	0.95 (0.38–2.41)
Nimodipine prophylaxis	0.12 (0.03–0.55)	0.06 (0.01–0.35)
Intraparenchymal Hematoma	2.83 (1.41–5.70)	3.32 (1.28–8.58)
Combined ICP/$PbtO_2$guided therapy	2.83 (1.41–5.70)	0.55 (0.20–1.46)

WFNS : world federation of neurological surgeons; ICP: intracranial hypertension; $PbtO_2$: brain tissue oxygenation; DCI = delayed cerebral ischemia.

Hospital mortality and $PbtO_2$ guided therapy

Non-survivors had higher severity scores on admission, suffered from often from chronic respiratory obstructive disease and cancer, received more frequently vasopressors and mechanical ventilation, were more often treated with surgical clipping, developed more complications (i.e. re-bleeding, hydrocephalus, intracranial hypertension and DCI) and underwent more specific therapies (i.e. osmotic therapy, barbituric coma and induced hypothermia) than survivors (Supplemental Table S1). However, the proportion of patients receiving $PbtO_2$-guided therapy (26/68, 38% vs. 28/95, 30%; p = 0.31) was similar between the two groups. In the Cox regression analysis adjusted for age, endovascular treatment, intracranial hypertension, DCI, intraparenchymal hematoma and nimodipine prophylaxis, combined ICP/$PbtO_2$-guided therapy (HR 1.11 [0.67–1.84]; Supplemental Table S2) was not independently associated with hospital mortality.

ICP- vs. ICP/$PbtO_2$-guided therapy

Among the 102 patients that received a therapy based on invasive neuromonitoring (either ICP only or ICP/$PbtO_2$-guided therapy), 75 (74%) had UO. Patients with UO received less prophylactic nimodipine and

were less treated with endovascular coiling; also, they also had more episodes of intracranial hypertension (Supplemental Table S2). In the multivariable analysis adjusted for endovascular treatment and nimodipine prophylaxis, $PbtO_2$ guided therapy was associated with a lower risk of UO (OR 0.33 [95% 0.12–0.90]) in 6 months (Table 3). In this subgroup of patients, hospital mortality was 56%; non-survivors had more frequently episodes of intracranial hypertension than others. In the Cox regression analysis, $PbtO_2$-guided therapy (HR 0.70 [0.41–1.19]; Supplemental Table S4) was not associated with survival.

Table 3
Logistic regression analysis to identify possible association between combined ICP/$PbtO_2$ guided therapy and 6-month unfavorable neurologic outcome in patients undergoing ICP- or ICP/$PbtO_2$ guided-therapy (n = 102). Data are reported as odds ratio (OR) and 95 % confidence intervals (CIs).

	Univariable analysis	**Multivariable analysis**
	OR (95% CI)	**OR (95% CI)**
Combined ICP/$PbtO_2$ guided therapy	0.29 (0.11–0.77)	0.33 (0.12–0.90)
Nimodipine	0.14 (0.02–1.23)	0.23 (0.03–1.98)
Endovascular (coiling) therapy	0.31 (0.10–0.89)	0.47 (0.15–1.49)
ICP: intracranial hypertension; $PbtO_2$: brain tissue oxygenation.		

Tissue hypoxia and outcome

Among patients undergoing $PbtO_2$ monitoring, both those with UO and non-survivors had a higher burden of hypoxia, more episodes of intracranial hypertension and experienced re-bleeding more frequently than the others (Supplemental Table S5). Figure 2 shows the time-course of $PbtO_2$ levels during ICU stay according to neurological outcome (Fig. 2A) or hospital mortality (Fig. 2B). In the logistic regression model, both brain hypoxia (OR 12.26 [95% CIs 1.21-124.48]) and severe brain hypoxia (OR 4.51 [95% CI 1.17–17.45]) were associated with UO; moreover, the burden of hypoxia (AUC $PbtO_2$ x time; OR 1.003 [95% CIs 1.001–1.005]) was also a factor associated with UO whereas PbtO2 guided therapy had no impact on outcome when adjusted for the presence of hypoxia and intracranial hypertension (Supplemental Tables 6–8). In the multivariable Cox regression analysis brain tissue hypoxia was not associated with hospital mortality. Interestingly, PbtO2 guided therapy reduced the risk of dying (HR 0.35 [95% CI 0.13–0.95]) when adjusted for brain hypoxia and intracranial hypertension (Supplemental Table S9).

Discussion

In this retrospective single-center cohort of patients with non-traumatic spontaneous SAH, the early use of ICP/$PbtO_2$ guided therapy compared to patients that received no therapy or ICP only guide therapy was not associated with an improved outcome. Only in patients requiring a therapy driven by MMM (i.e. ICP or

combined ICP/$PbtO_2$), $PbtO_2$-guided therapy was associated with a lower risk of UO than ICP-guided therapy. Brain hypoxia was independently associated with a poor neurological outcome. In patients monitored with PbtO2 catheters, PbtO2 guided therapy was associated with a lesser risk of death.

MMM has been widely advocated to assess poor grade neurocritical patients, since the severity of the initial injury or the concomitant use of sedation and/or neuromuscular blockade significantly reduce the reliability of clinical examination to detect neurologic deterioration or tissue hypoxia.[14] $PbtO_2$ monitoring provide focal but clinically relevant information on tissue oxygenation and, if adequately interpreted and included into a therapeutic protocol, could act as an early trigger to initiate therapies even in the presence of normal ICP values.[17] This is even more relevant in SAH patients, as sustained and severe increase of ICP are less frequent than in TBI patients and tissue hypoxia can be driven by other mechanisms than cerebral swelling, such as diffuse hypoperfusion or delayed vasoconstriction.[17]

Brain oxygen values reflect an equilibrium between oxygen delivery (i.e. cerebral blood flow, hemoglobin and arterial oxygenation), consumption (i.e. brain metabolism, mitochondria and body temperature) and extraction (microcirculation and blood-brain barrier).[38,39] In SAH patients, low $PbtO_2$ has been associated with different pathologic pathways, such as low cerebral blood flow,[30,40] lung injury with hypoxemia[22,41] and/or anemia.[42] As such, strategies aiming at increasing cerebral blood flow, using high inspired oxygen fraction on the ventilator or prescribing red blood cell transfusion can increases $PbtO_2$ levels in some of these patients.[44,43] However, low $PbtO_2$ levels do not necessarily represent tissue ischemia[38] and some studies failed to show an association between low $PbtO_2$ and unfavorable outcomes.[44,45] In our study, episodes of PbtO2 < 20 mmHg and < 10 mmHg were associated with unfavorable neurological outcome but not mortality, perhaps because PbtO2 guided therapy successfully improved survival in the cohort of patients monitored with combined ICP/$PbtO_2$. Future studies should evaluate in larger cohorts the optimal threshold of $PbtO_2$ to predict poor neurological outcome and mortality and therefore optimize therapies in SAH patients. The integration of ICP/$PbtO_2$ monitoring with other tools (i.e. electroencephalography, cerebral microdialysis) should therefore be considered as a useful MMM approach to precisely define the pathophysiology of brain injury and individualize clinical management in SAH patients, although additional data are necessary to understand its role on modifying patients' outcome.[14,46]

In TBI patients, Okonkwo et al. [26] showed that the use of $PbtO_2$ guided therapy using a specific and complex protocol reduced the burden of brain hypoxia when compared to patients that underwent ICP guided therapy only. Furthermore, two meta-analysis reported that ICP/$PbtO_2$ guided therapy was associated with improved neurologic outcome, when compared with standard ICP-guided therapy[47,48]; although large randomized trials in TBI patients are currently ongoing to provide more robust evidence. In our study, the burden of brain hypoxia remains relatively high despite of protocolized $PbtO_2$-guided therapy. In another study, Rass et al. 2019 [44] also showed similar results: 81% of SAH patients included in two experienced centers had at least one episode of brain hypoxia (i.e.$PbtO_2$ < 20mmHg). This could

explain why we could not find an association of $PbtO_2$-guided therapy compared to no therapy and/or ICP-guided therapy with an improvement in neurological outcome, since the proposed treatment may not be enough to reverse tissue hypoxia, even in the presence of protocolized strategies. Moreover, we lack robust data showing which intervention (i.e. raising blood pressure, transfusions, changes in $PaCO_2$ or body temperature etc.) is the most effective to correct brain hypoxia in SAH patients. Also, as brain hypoxia can occur either in the early phase but also after several days since admission because of DCI, the lack of adequate evidence supporting effective therapeutic strategies to treat DCI would also limit the effectiveness of $PbtO_2$-guided therapies in this setting.

Some patients had normal ICP and $PbtO_2$ values and required no intervention; moreover, as the monitoring itself cannot improve outcome alone since the decision to treat is ultimately at the clinician's discretions we performed an additional analysis including only those patients where an intervention was undertaken, either guided by ICP alone or by ICP/$PbtO_2$. In this subgroup of patients, $PbtO_2$-guided therapy was associated with a favorable neurological outcome when compared to ICP-guided therapy. In a before/after study, Veldeman et al. showed that the implementation of $PbtO_2$ and microdialysis monitoring in poor grade SAH patients was associated with an earlier detection of DCI and a significant reduction in the occurrence of UO, from 60–46%.[49] In another before/after study including good grade SAH patients with secondary deterioration, the introduction of invasive neuromonitoring ($PbtO_2$ and microdialysis) was associated a significant reduction of silent cerebral infarctions, although no significant effects on neurological outcome was observed.[50] However, as the introduction of neuromonitoring could also been associated with other significant changes in diagnostic procedure and patients' management (i.e. before and after study), it is difficult to conclude the effectiveness of invasive neuromonitoring on patients' outcome from these studies.

Our study has some limitations. First due to its retrospective design, some deviations from protocolized care or decisions to tolerate quite low $PbtO_2$ values (i.e. 15–20 mmHg) in case of improvement of clinical status and/or awakening could not be adequately addressed. Second, the number of patients receiving $PbtO_2$ monitoring was relatively limited, which may have reduced the power for future statistical adjustment to assess smaller effects of $PbtO_2$ monitoring on patients' outcome. Third, as this cohort reflected the experience of a single center, generalizability of our findings might be limited. Finally, we did not specifically report all single therapeutic interventions and their effects on $PbtO_2$ values over time.

Conclusions

In this cohort of SAH patients, brain hypoxia was associated with poor neurological outcome. PbtO2-guided therapy was associated with better neurological recovery in the subgroup of patients requiring therapeutic interventions driven by neuromonitoring (ICP alone or ICP/$PbtO_2$). Prospective studies are needed to properly assess the role of combined ICP/$PbtO_2$ monitoring and $PbtO_2$-guided therapy in SAH patients.

Declarations

Data Availability statement

Due to ethical restrictions, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated after the analysis during this study are included in this published article and its supplementary information files.

Authors' contributions statement:

EGB and FST conceived the study; EGB, DD, NND, MM, MT, SB, MAB and JA selected the population and collected the data; EGB, LP and FST conducted the statistical analysis and wrote the first draft of the paper; JLV, JC, SS, OD, SB revised the text for intellectual content. All authors read and approved the final manuscript.

Additional Information

Ethics approval and consent to participate: The study protocol was approved by the Erasme Hospital (Université Libre de Bruxelles) ethics committee (P2019/649) and the informed written consent was waived due to the retrospective design of the study. All methods were carried out in accordance with relevant scientific and ethical guidelines and regulations.

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests regarding this manuscript.

Funding: No funding was obtained to this study.

Acknowledgements: We thank Hassane Njimi Msc PhD for his invaluable help with the statistical analysis.

References

1. Mozaffarian, D. *et al.* Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation.***131**, e29–322 https://doi.org/10.1161/CIR.0000000000000152 (2015).
2. Krishnamurthi, R. V. *et al.* Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health.***1**, e259–281 https://doi.org/10.1016/S2214-109X(13)70089-5 (2013).
3. Connolly, E. S. Jr. *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke.***43**, 1711–1737 https://doi.org/10.1161/STR.0b013e3182587839 (2012).

4. Grote, E. & Hassler, W. The critical first minutes after subarachnoid hemorrhage. *Neurosurgery.***22**, 654–661 https://doi.org/10.1227/00006123-198804000-00006 (1988).
5. Hayman, E. G., Wessell, A., Gerzanich, V., Sheth, K. N. & Simard, J. M. Mechanisms of Global Cerebral Edema Formation in Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care.***26**, 301–310 https://doi.org/10.1007/s12028-016-0354-7 (2017).
6. Cahill, J., Calvert, J. W. & Zhang, J. H. Mechanisms of early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.***26**, 1341–1353 https://doi.org/10.1038/sj.jcbfm.9600283 (2006).
7. Heuer, G. G., Smith, M. J., Elliott, J. P., Winn, H. R. & LeRoux, P. D. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg.***101**, 408–416 https://doi.org/10.3171/jns.2004.101.3.0408 (2004).
8. Macdonald, R. L., Pluta, R. M. & Zhang, J. H. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Clin Pract Neurol.***3**, 256–263 https://doi.org/10.1038/ncpneuro0490 (2007).
9. Chesnut, R., Videtta, W., Vespa, P. & Le Roux, P. & Participants in the International Multidisciplinary Consensus Conference on Multimodality, M. Intracranial pressure monitoring: fundamental considerations and rationale for monitoring. *Neurocrit Care***21 Suppl 2**, S64-84, doi:10.1007/s12028-014-0048-y (2014).
10. Zoerle, T. *et al.* Intracranial pressure after subarachnoid hemorrhage. *Crit Care Med.***43**, 168–176 https://doi.org/10.1097/CCM.0000000000000670 (2015).
11. Stiefel, M. F. *et al.* Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg.***103**, 805–811 https://doi.org/10.3171/jns.2005.103.5.0805 (2005).
12. De Georgia, M. A. Brain Tissue Oxygen Monitoring in Neurocritical Care. *J Intensive Care Med.***30**, 473–483 https://doi.org/10.1177/0885066614529254 (2015).
13. van den Brink, W. A. *et al.* Brain oxygen tension in severe head injury. *Neurosurgery.***46**, 868–876 discussion 876 – 868 https://doi.org/10.1097/00006123-200004000-00018 (2000).
14. Le Roux, P. *et al.* Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med***40**, 1189–1209, doi:10.1007/s00134-014-3369-6 (2014).
15. Bouzat, P. *et al.* Accuracy of brain multimodal monitoring to detect cerebral hypoperfusion after traumatic brain injury*. *Crit Care Med.***43**, 445–452 https://doi.org/10.1097/CCM.0000000000000720 (2015).
16. Citerio, G., Oddo, M. & Taccone, F. S. Recommendations for the use of multimodal monitoring in the neurointensive care unit. *Curr Opin Crit Care.***21**, 113–119 https://doi.org/10.1097/MCC.0000000000000179 (2015).

17. Francoeur, C. L. & Mayer, S. A. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care.***20**, 277 https://doi.org/10.1186/s13054-016-1447-6 (2016).
18. Proust, F., Hannequin, D., Langlois, O., Freger, P. & Creissard, P. Causes of morbidity and mortality after ruptured aneurysm surgery in a series of 230 patients. The importance of control angiography. *Stroke.***26**, 1553–1557 https://doi.org/10.1161/01.str.26.9.1553 (1995).
19. Ropper, A. H. & Zervas, N. T. Outcome 1 year after SAH from cerebral aneurysm. Management morbidity, mortality, and functional status in 112 consecutive good-risk patients. *J Neurosurg.***60**, 909–915 https://doi.org/10.3171/jns.1984.60.5.0909 (1984).
20. Lee, H. *et al.* Clinical prediction of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 1–8 https://doi.org/10.3171/2018.1.JNS172715 (2018).
21. Helbok, R. *et al.* Intracerebral monitoring of silent infarcts after subarachnoid hemorrhage. *Neurocrit Care.***14**, 162–167 https://doi.org/10.1007/s12028-010-9472-9 (2011).
22. Chen, H. I. *et al.* Detection of cerebral compromise with multimodality monitoring in patients with subarachnoid hemorrhage. *Neurosurgery.***69**, 53–63 discussion 63 https://doi.org/10.1227/NEU.0b013e3182191451 (2011).
23. Oddo, M. *et al.* Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery.***69**, 1037–1045 discussion 1045 https://doi.org/10.1227/NEU.0b013e3182287ca7 (2011).
24. Bardt, T. F. *et al.* Monitoring of brain tissue PO2 in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta Neurochir Suppl.***71**, 153–156 (1998).
25. Maloney-Wilensky, E. *et al.* Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med.***37**, 2057–2063 https://doi.org/10.1097/CCM.0b013e3181a009f8 (2009).
26. Okonkwo, D. O. *et al.* Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. *Crit Care Med.***45**, 1907–1914 https://doi.org/10.1097/CCM.0000000000002619 (2017).
27. Spiotta, A. M. *et al.* Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *J Neurosurg.***113**, 571–580 (2010).
28. Narotam, P. K., Morrison, J. F. & Nathoo, N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *J Neurosurg.***111**, 672–682 https://doi.org/10.3171/2009.4.JNS081150 (2009).
29. Kett-White, R. *et al.* Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. *Neurosurgery.***50**, 1213–1221 discussion 1221 – 1212 https://doi.org/10.1097/00006123-200206000-00008 (2002).
30. Vath, A., Kunze, E., Roosen, K. & Meixensberger, J. Therapeutic aspects of brain tissue pO2 monitoring after subarachnoid hemorrhage. *Acta Neurochir Suppl.***81**, 307–309 (2002).

31. Bogossian, E. G. *et al.* The impact of extra-cerebral infection after subarachnoid hemorrhage: a single center cohort study. *World Neurosurg.*https://doi.org/10.1016/j.wneu.2020.09.102 (2020).
32. Vincent, J. L. *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.***22**, 707–710 (1996).
33. Knaus, W. A., Draper, E. A., Wagner, D. P. & Zimmerman, J. E. APACHE II: a severity of disease classification system. *Crit Care Med.***13**, 818–829 (1985).
34. Report of World Federation of Neurological Surgeons Committee on. a Universal Subarachnoid Hemorrhage Grading Scale. *J Neurosurg.***68**, 985–986 (1988).
35. Teasdale, G. & Jennett, B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.***2**, 81–84 (1974).
36. Frontera, J. A. *et al.* Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery***59**, 21–27; discussion 21–27, doi:10.1227/01.NEU.0000218821.34014.1B (2006).
37. Jennett, B. & Bond, M. Assessment of outcome after severe brain damage. *Lancet.***1**, 480–484 https://doi.org/10.1016/s0140-6736(75)92830-5 (1975).
38. Rose, J. C., Neill, T. A. & Hemphill, J. C. 3 Continuous monitoring of the microcirculation in neurocritical care: an update on brain tissue oxygenation. *Curr Opin Crit Care.***12**, 97–102 https://doi.org/10.1097/01.ccx.0000216574.26686.e9 (2006).
39. Soehle, M., Jaeger, M. & Meixensberger, J. Online assessment of brain tissue oxygen autoregulation in traumatic brain injury and subarachnoid hemorrhage. *Neurol Res.***25**, 411–417 https://doi.org/10.1179/016164103101201580 (2003).
40. Jaeger, M., Soehle, M., Schuhmann, M. U., Winkler, D. & Meixensberger, J. Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. *Acta Neurochir (Wien).***147**, 51–56 discussion 56 https://doi.org/10.1007/s00701-004-0408-z (2005).
41. Reinprecht, A. *et al.* Prone position in subarachnoid hemorrhage patients with acute respiratory distress syndrome: effects on cerebral tissue oxygenation and intracranial pressure. *Crit Care Med.***31**, 1831–1838 https://doi.org/10.1097/01.CCM.0000063453.93855.0A (2003).
42. Smith, M. J. *et al.* Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med.***33**, 1104–1108 https://doi.org/10.1097/01.ccm.0000162685.60609.49 (2005).
43. Kurtz, P. *et al.* The Effect of Packed Red Blood Cell Transfusion on Cerebral Oxygenation and Metabolism After Subarachnoid Hemorrhage. *Neurocrit Care.***24**, 118–121 https://doi.org/10.1007/s12028-015-0180-3 (2016).
44. Rass, V. *et al.* Protocolized Brain Oxygen Optimization in Subarachnoid Hemorrhage. *Neurocrit Care.***31**, 263–272 https://doi.org/10.1007/s12028-019-00753-0 (2019).
45. Barth, M. *et al.* Correlation of clinical outcome with pressure-, oxygen-, and flow-related indices of cerebrovascular reactivity in patients following aneurysmal SAH. *Neurocrit Care.***12**, 234–243 https://doi.org/10.1007/s12028-009-9287-8 (2010).

46. Sandsmark, D. K., Kumar, M. A., Park, S. & Levine, J. M. Multimodal monitoring in subarachnoid hemorrhage. *Stroke.***43**, 1440–1445 https://doi.org/10.1161/STROKEAHA.111.639906 (2012).
47. Xie, Q., Wu, H. B., Yan, Y. F., Liu, M. & Wang, E. S. Mortality and Outcome Comparison Between Brain Tissue Oxygen Combined with Intracranial Pressure/Cerebral Perfusion Pressure-Guided Therapy and Intracranial Pressure/Cerebral Perfusion Pressure-Guided Therapy in Traumatic Brain Injury: A Meta-Analysis. *World Neurosurg.***100**, 118–127 https://doi.org/10.1016/j.wneu.2016.12.097 (2017).
48. Nangunoori, R. *et al.* Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: a systematic literature review. *Neurocrit Care.***17**, 131–138 https://doi.org/10.1007/s12028-011-9621-9 (2012).
49. Veldeman, M. *et al.* Invasive neuromonitoring with an extended definition of delayed cerebral ischemia is associated with improved outcome after poor-grade subarachnoid hemorrhage. *J Neurosurg.* 1–8 https://doi.org/10.3171/2020.3.JNS20375 (2020).
50. Veldeman, M. *et al.* Treatment of Delayed Cerebral Ischemia in Good-Grade Subarachnoid Hemorrhage: Any Role for Invasive Neuromonitoring? *Neurocrit. Care.*https://doi.org/10.1007/s12028-020-01169-x (2020).

Figures

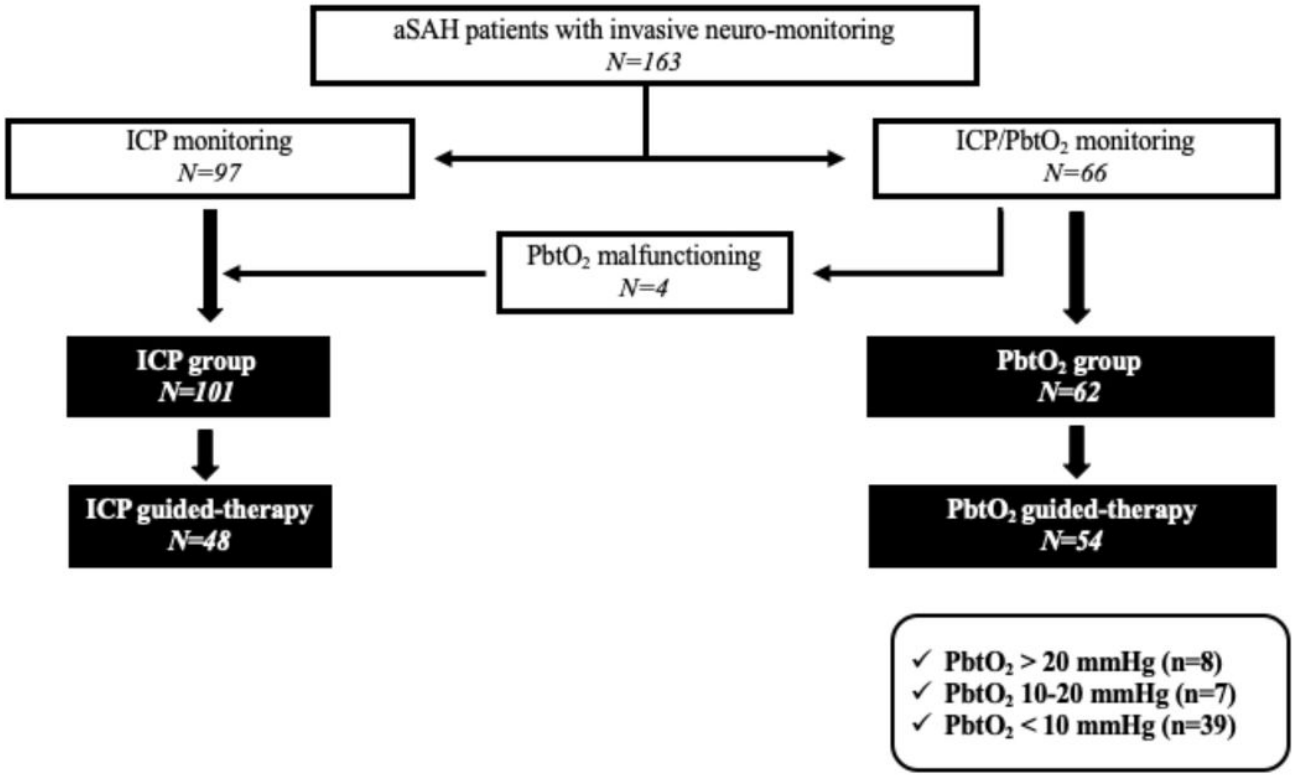

Figure 1

Flow-chart of the study. SAH: subarachnoid hemorrhage; ICP: intracranial pressure; PbtO2: brain tissue oxygenation

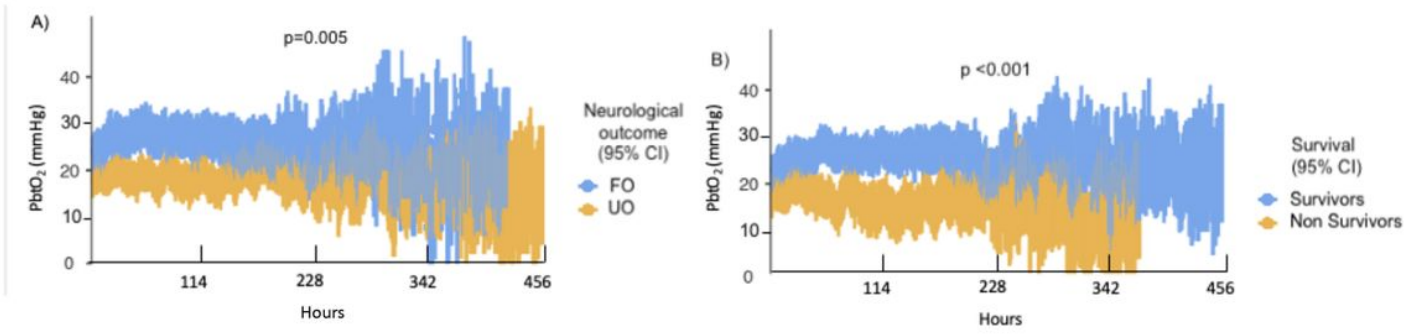

Figure 2

All patients were included in this analysis. Brain oxygen pressure (PbtO2) was automatically measured every minute and 1-hour median was calculated to plot the values of each hour in the x-axis. PbtO2 values were measured in mmHg and time is expressed in hours. Panel A: Brain oxygen pressure (PbtO2) time-course in patients with favorable (FO) and unfavorable (UO) neurological outcome. Panel B: Brain oxygen pressure (PbtO2) time-course in survivors and non-survivors.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Eletronicsupplementalmaterial.docx