Optimal Cerebral Perfusion Pressure Guided by Brain Oxygen Pressure Measurement

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Background: Although increasing cerebral perfusion pressure (CPP) is commonly accepted to improve brain tissue oxygen pressure (PbtO₂), it remains unclear whether recommended CPP targets (i.e., >60 mmHg) would result in adequate brain oxygenation in brain injured patients. The aim of this study was to identify the target of CPP associated with normal brain oxygenation.

Methods: Prospectively collected data including patients suffering from acute brain injury and monitored with PbtO₂, in whom daily CPP challenge using vasopressors was performed. Initial CPP target was >60 mmHg; norepinephrine infusion was modified to have an increase in CPP of at least 10 mmHg at two different steps above the baseline values. Whenever possible, the same CPP challenge was performed for the following days, for a maximum of 5 days. CPP “responders” were patients with a relative increase in PbtO₂ from baseline values > 20%.

Results: A total of 53 patients were included. On the first day of assessment, CPP was progressively increased from 73 (70–76) to 83 (80–86), and 92 (90–96) mmHg, which resulted into a significant PbtO₂ increase [from 20 (17–23) mmHg to 22 (20–24) mmHg and 24 (22–26) mmHg, respectively; p < 0.001]. Median CPP value corresponding to PbtO₂ values > 20 mmHg was 79 (74–87) mmHg, with 2 (4%) patients who never achieved such target. Similar results of CPP targets were observed the following days. A total of 25 (47%) were PbtO₂ responders during the CPP challenge on day 1, in particular if low PbtO₂ was observed at baseline.

Conclusions: PbtO₂ monitoring can be an effective way to individualize CPP values to avoid tissue hypoxia. Low PbtO₂ values at baseline can identify the responders to the CPP challenge.

Keywords: brain injury, brain oxygenation, optimal perfusion, individualized therapy, traumatic brain injury, intracranial hemorrhage, subarachnoid hemorrhage
INTRODUCTION

Monitoring of patients with critical illness has expanded significantly over the past several decades. As for hemodynamics, respiratory or renal functions, several studies have underlined the importance of monitoring brain function, not only in patients with a primary brain injury [i.e., traumatic brain injury (TBI)], subarachnoid hemorrhage (SAH), post-anoxic brain injury], but also in those with a systemic disease, such as sepsis, acute pancreatitis, or cardiogenic shock, who may present different alterations of cerebral function and potentially may develop secondary brain injuries (1), which can impact on long-term functional and cognitive recovery (2).

In patients suffering from TBI, the combination of intracranial pressure (ICP) and cerebral perfusion pressure (CPP)-guided therapy is recommended for the current management of these patients (3); similarly, ICP and CPP are the cornerstone of management of severe non-traumatic brain injury patients, although the evidence suggesting that such approach might impact on long-term outcomes remain limited (4). Importantly, increased ICP could be a late and insensitive indicator of some secondary brain injuries (5, 6); in particular, the occurrence of tissue hypoxia may occur even in the absence of intracranial hypertension and, when untreated or refractory to therapeutic interventions, is associated with an increased risk of poor neurological outcome in brain injured patients (7, 8). As such, rather than protocolizing therapies to target fixed ICP and CPP values for all patients, independently from the underlying brain injury, comorbid diseases, and the severity of brain edema, the implementation of brain tissue oxygen pressure (PbtO₂) monitoring could be helpful to individualize ICP and CPP values based on cerebral oxygenation.

Although higher than recommended CPP targets (i.e., >60 mmHg) have been associated with adequate PbtO₂ values in heterogeneous populations of brain injured patients, few prospective studies have evaluated the effects of increasing CPP using vasopressors on PbtO₂ in such patients. In one small study (n = 11) on TBI patients, increasing CPP from 70 to 90 mmHg with norepinephrine resulted in a significant increase in PbtO₂ (from 17 ± 8 to 22 ± mmHg), despite brain metabolism was only marginally affected (8). In another study including 14 TBI patients, increasing CPP resulted also in a significant increase in PbtO₂, although this was measured after a challenge of inspired oxygen at 100% on the ventilator (9). However, all these studies did not specifically investigate the proportion of patients requiring higher than recommended CPP to obtain adequate PbtO₂ values, neither whether this CPP target would change along the hospital stay.

The aim of this study was therefore to evaluate which level of CPP corresponds to an adequate PbtO₂ in an heterogeneous population of brain injured patients. Secondary aims were to assess: (a) whether this level of CPP change over time and (b) the characteristics of patients requiring higher than recommended CPP targets to have optimal brain oxygenation values.

METHODS

Study Population

This was an analysis of prospectively collected data including all adult (>18 years of age) patients with an acute primary brain injury admitted to the ICU of Erasme Hospital, Brussels, Belgium, between January 2016 and December 2020. Eligible patients were those: (a) having a PbtO₂ monitoring catheter, which was inserted according to the decision of senior ICU physician and an experienced neurosurgeon; (b) receiving vasopressors to target a CPP of at least 60–70 mmHg; (c) who underwent daily CPP challenge as part of routine patient management (see below). Data for all measurements were recorded into the patient management data system (PDMS, Picis Critical Care Manager; Picis Inc., Wakefield, MA, USA). Exclusion criteria were a malfunctioning PbtO₂ catheter, the absence of vasopressor therapy, elevated ICP (>25 mmHg) refractory to different interventions (i.e., sedation, osmotic therapy, and hyperventilation), clinical contraindication to increased CPP (i.e., frequent arrhythmias or acute heart failure).

The study was approved by the ethical committee of the Erasme Hospital (Comité d’Ethique Hospitalo-Facultaire Erasme – ULB; P2021/038), which waived the need of informed consent given the observational design of the study analyzing recorded data into the PDMS.

Patients’ Management and CPP Challenge

Patients were managed according to local protocols, based on international recommendations (3, 4, 10, 11). A triple lumen bolt allowing the insertion of a PbtO₂ probe (IM3.ST_EU; Integra LifeSciences Corporation, Plainsboro, NJ, USA), alone or in association with an eight-contact depth EEG electrode and a microdialysis catheter, was placed in the operating room by a neurosurgeon in patients with TBI, subarachnoid hemorrhage (SAH), or intracranial hemorrhage (ICH), who had indications for ICP monitoring (i.e., abnormal CT-scan findings and a Glasgow Coma Score on admission < 9). The bolt was positioned in the normal-appearing brain area of the injured side or, in case of aneurysmal SAH, on either the ipsilateral side of the aneurysm (i.e., anterior circulation) or on the right side (i.e., no aneurysm identified or aneurysm located in the posterior circulation). Other continuously monitored variables included electrocardiogram, mean arterial pressure (MAP), peripheral oxygen saturation, end-tidal carbon dioxide and body temperature (i.e., with urinary or esophageal probes), as a routine approach in all severe brain injured patients.

For patients requiring vasopressors, initial CPP and PbtO₂ targets are >60 mmHg and >20 mmHg, respectively. Cerebral perfusion pressure (CPP) was calculated as the difference between MAP and ICP; MAP was zeroed at the level of the left atrium (i.e., with patient at 30° recumbent position). After the initial daily assessment of the patient, which can also include the evaluation of pupillary function using an automated pupillometry (NeurOptics NPI-200; Neuropoint, Irvine, CA, USA) to calculate the Neurological Pupil Index (NPI), or brain flow velocities with Transcranial Doppler (TCD) to measure mean flow velocities (mFV) and the pulsatility index (PI) (12),
### TABLE 1 | Characteristics of study population, according to neurological outcome (UO, unfavorable; FO, favorable).

| Characteristics                      | Overall (n = 53) | UO (n = 33) | FO (n = 20) | p-value |
|---------------------------------------|------------------|-------------|-------------|---------|
| **Demographics**                      |                  |             |             |         |
| Age, years                            | 50 (40–58)       | 51 (44–58) | 47 (38–57) | 0.45    |
| Male gender, n (%)                    | 31 (58)          | 19 (58)    | 12 (60)    | 1.00    |
| **Comorbidities**                     |                  |             |             |         |
| Hypertension, n (%)                   | 14 (26)          | 10 (30)    | 4 (20)     | 0.53    |
| Heart disease, n (%)                  | 2 (4)            | 0          | 2 (10)     | 0.14    |
| Alcohol, n (%)                        | 12 (23)          | 7 (21)     | 5 (25)     | 0.75    |
| Smoking, n (%)                        | 12 (23)          | 6 (18)     | 6 (30)     | 0.34    |
| Diabetes, n (%)                       | 7 (13)           | 5 (15)     | 2 (10)     | 0.70    |
| Previous neurological disease, n (%)  | 2 (4)            | 1 (3)      | 1 (5)      | 1.00    |
| CKD, n (%)                            | 0                | 0          | 0          | -       |
| COPD, n (%)                           | 4 (8)            | 3 (9)      | 1 (5)      | 1.00    |
| Immunosuppression, n (%)              | 0                | 0          | 0          | -       |
| Cancer, n (%)                         | 3 (6)            | 3 (9)      | 0          | 0.28    |
| Liver cirrhosis, n (%)                | 1 (2)            | 1 (3)      | 0          | 1.00    |
| **On admission**                      |                  |             |             |         |
| Glasgow coma scale                    | 7 (3–10)         | 5 (3–9)    | 7 (5–13)   | 0.14    |
| **Type of disease, n (%)**            |                  |             |             | 0.25    |
| TBI                                   | 20 (38)          | 10 (30)    | 10 (50)    |         |
| SAH                                   | 29 (55)          | 21 (64)    | 8 (40)     |         |
| ICH                                   | 4 (8)            | 2 (6)      | 2 (10)     |         |
| **During ICU stay**                   |                  |             |             |         |
| Vasopressors, n (%)                   | 53 (100)         | 33 (100)   | 20 (100)   | -       |
| Mechanical ventilation, n (%)         | 53 (100)         | 33 (100)   | 20 (100)   | -       |
| RRT, n (%)                            | 1 (2)            | 1 (3)      | 0          | 1.00    |
| Osmotic therapy, n (%)                | 45 (85)          | 29 (88)    | 16 (80)    | 0.46    |
| Decompressive craniectomy, n (%)      | 10 (19)          | 5 (15)     | 5 (25)     | 0.48    |
| Hypothermia, n (%)                    | 10 (19)          | 9 (27)     | 1 (5)      | 0.07    |
| Anti-epileptics, n (%)                | 48 (91)          | 29 (88)    | 19 (95)    | 0.64    |
| Barbiturates, n (%)                   | 21 (40)          | 16 (48)    | 5 (25)     | 0.15    |
| Intracranial hypertension, n (%)      | 36 (68)          | 26 (79)    | 10 (50)    | 0.04    |
| Seizures, n (%)                       | 9 (17)           | 5 (15)     | 4 (20)     | 0.72    |
| **On the first day of assessment**    |                  |             |             |         |
| Body temperature, °C                  | 37 (36.8–37.3)   | 36 (36.8–37.3) | 36.9 (36.7–37.3) | 0.72   |
| PaCO<sub>2</sub>, mmHg                | 37 (36–39)       | 37 (36–39) | 37 (36–38) | 0.95    |
| PaO<sub>2</sub>, mmHg                 | 102 (98–110)     | 104 (98–108) | 104 (99–111) | 0.38   |
| Lactate, mmol/L                       | 1 (0.8–1.2)      | 1 (0.8–1.2) | 1.0 (0.8–1.1) | 0.25   |
| Hemoglobin, g/dl                      | 11.3 (10.8–12.2) | 11.2 (10.8–12.1) | 11.4 (10.9–12.2) | 0.88   |
| FVm MCA, cm/sec                       | 55.3 (45.8–65)   | 51.7 (47.5–67.3) | 58.0 (54.7–65.2) | 0.46   |
| Pulsatility Index                     | 0.90 (0.73–1.05) | 0.93 (0.73–1.08) | 0.85 (0.73–1.04) | 0.77   |

(Continued)
TABLE 2 | Changes in study variables on the first day of assessment, according to different steps of mean arterial pressure (MAP) and neurological outcome (UO, unfavorable; FO, favorable).

|                | Step 1 | Step 2 | Step 3 | p-value |
|----------------|--------|--------|--------|---------|
| All (n = 53)   |        |        |        |         |
| MAP, mmHg      | 83 (82–89) | 95 (91–99) | 105 (100–109) | <0.01 |
| ICP, mmHg      | 12 (8–14) | 12 (9–15) | 11 (9–15) | <0.01 |
| CPP, mmHg      | 73 (70–76) | 83 (80–86) | 92 (90–96) | <0.01 |
| PbtO₂, mmHg    | 20 (17–23) | 22 (20–24) | 24 (22–26) | <0.01 |
| UO (n = 33)    |        |        |        |         |
| MAP, mmHg      | 83 (81–87) | 93 (91–96) | 103 (100–110) | <0.01 |
| ICP, mmHg      | 10 (6–14) | 11 (7–14) | 11 (9–15) | <0.01 |
| CPP, mmHg      | 73 (70–75) | 82 (79–85) | 91 (89–96) | <0.01 |
| PbtO₂, mmHg    | 19 (16–23) | 22 (19–24) | 24 (22–26) | <0.01 |
| FO (n = 20)    |        |        |        |         |
| MAP, mmHg      | 86 (82–90) | 97 (94–100) | 107 (102–110) | <0.01 |
| ICP, mmHg      | 13 (10–17) | 12 (10–17) | 13 (10–17) | 0.42 |
| CPP, mmHg      | 74 (70–77) | 85 (81–88) | 93 (91–96) | <0.01 |
| PbtO₂, mmHg    | 21 (18–24) | 22 (21–25) | 24 (23–28) | <0.01 |

UO, unfavorable outcome; FO, favorable outcome; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; PbtO₂, brain tissue oxygenation.

outcome (FO) was considered as a GOS 4–5, while unfavorable outcome (UO) as GOS 1–3.

Study Outcomes
The primary outcome of the study was to evaluate which level of CPP corresponds to a PbtO₂ ≥ 20 mmHg. Secondary outcomes included: (a) proportion and characteristics of PbtO₂ responders; (b) comparison of PbtO₂ changes according to the presence of baseline tissue hypoxia; (c) comparison of PbtO₂ changes over time; (d) association of PbtO₂ changes with NPi, mFV, and/or PI changes; (e) differences in PbtO₂ changes during CPP challenges according to neurological outcome.

Statistical Analysis
Data were analyzed using R statistical software version 4.0.3 (R Foundation for Statistical Computing), Prism (GraphPad Software Inc.), and IBM SPSS Statistics for Macintosh 27 (Armonk, NY, USA). Categorical variables were expressed as count (percentage) and continuous variables as mean ± standard deviation (SD) or median (25th–75th percentiles). The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify the normality of distribution of continuous variables. Differences between groups were assessed using the chi-square test or Fisher’s exact test for categorical variables and Student’s t-test, or Mann–Whitney U-test for continuous variables, as appropriate. Mixed model procedure with restricted maximum likelihood (REML) estimation and “unstructured” covariance structure was used to examine the differences in PbtO₂ changes during CPP challenges over different days of assessment. All tests are two tailed and the statistical significance was set at the 5% level.

RESULTS

Study Population
Over a total of 162 patients, 109 were excluded (i.e., n = 49, not on vasopressors during the PbtO₂ monitoring period; n = 29, refractory intracranial hypertension; n = 31, measurements not performed) and 53 were eventually included into the final analysis. No significant differences were observed between included and excluded patients (Supplementary Table 1), except for a shorter ICU length of stay and higher mortality for the excluded group. Characteristics of the study population are shown in Table 1; the most frequent brain injury was SAH (n = 29, 55%). Hospital mortality occurred in 18 (34%) of patients, while 33 (62%) presented with UO.

CPP Challenge and PbtO₂
On the first day of assessment, baseline PbtO₂ and CPP were 20 (16–21) mmHg and 73 (70–76) mmHg, respectively; brain hypoxia at baseline was observed in 26 (49%) of patients.

FIGURE 1 | Cerebral perfusion pressure corresponding to a PbtO₂ > 20 mmHg (CPPox).
TABLE 3 | Characteristics of population according to PbtO2 responder or non-responder to CPP challenge.

| Demographics | Responder (n = 25) | Non-responder (n = 26) | p-value |
|--------------|------------------|-----------------------|---------|
| Age, years   | 52 (41–59)       | 50 (40–57)            | 0.57    |
| Male gender, n (%) | 11 (44)     | 20 (71)               | 0.06    |

| Comorbidities | Responder (n = 25) | Non-responder (n = 26) | p-value |
|---------------|--------------------|------------------------|---------|
| Hypertension, n (%) | 9 (36)           | 5 (18)                 | 0.21    |
| Heart disease, n (%) | 0 (0)            | 2 (7)                  | 0.49    |
| Alcohol, n (%) | 6 (24)            | 6 (21)                 | 1.00    |
| Smoking, n (%) | 8 (32)            | 4 (14)                 | 0.19    |
| Diabetes, n (%) | 2 (8)             | 5 (18)                 | 0.43    |
| Previous neurological disease, n (%) | 0 (0)         | 2 (7)                  | 0.49    |
| CKD, n (%)     | 0 (0)             | 0                      | –       |
| COPD, n (%)    | 1 (4)             | 3 (11)                 | 0.61    |
| Immunosuppression, n (%) | 0 (0)      | 0                      | –       |
| Cancer, n (%)  | 1 (4)             | 2 (7)                  | 1.00    |
| Liver Cirrhosis, n (%) | 1 (4)        | 0                      | 0.47    |

| On admission | Responder (n = 25) | Non-responder (n = 26) | p-value |
|--------------|--------------------|------------------------|---------|
| Glasgow coma scale | 6 (3–9)     | 7 (3–11)               | 0.59    |
| Type of disease, n (%) | 10 (40) | 10 (38)                | 0.65    |
| TBI           | 10 (40)           | 10 (38)                |         |
| SAH           | 14 (56)           | 15 (56)                |         |
| ICH           | 1 (4)             | 3 (10)                 |         |
| MED           | 0 (0)             | 0                      |         |

| During ICU stay | Responder (n = 25) | Non-responder (n = 26) | p-value |
|-----------------|--------------------|------------------------|---------|
| Vasopressors, n (%) | 25 (100)   | 28 (100)               | –       |
| Mechanical ventilation, n (%) | 25 (100) | 28 (100)               | –       |
| RRT, n (%)      | 1 (4)             | 0                      | 0.47    |
| Osmotic therapy, n (%) | 21 (84)  | 24 (88)                | 1.00    |
| Decompressive craniectomy, n (%) | 7 (28)  | 3 (11)                 | 0.16    |
| Hypothermia, n (%) | 4 (16)        | 6 (21)                 | 0.73    |
| Anti-epileptics, n (%) | 24 (96) | 24 (88)                | 0.36    |
| Barbiturates, n (%) | 12 (48)       | 9 (32)                 | 0.27    |
| Intracranial hypertension, n (%) | 19 (76)  | 17 (61)                | 0.26    |
| Seizures, n (%) | 4 (16)           | 5 (18)                 | 1.00    |

| On the first day of assessment | Responder (n = 25) | Non-responder (n = 26) | p-value |
|-------------------------------|--------------------|------------------------|---------|
| Body temperature, °C | 37.0 (36.8–37.3)   | 36.9 (36.7–37.4)       | 0.69    |
| PaCO2, mmHg | 38 (35–39)        | 37 (36–38)             | 0.51    |
| PaO2, mmHg   | 102 (98–110)      | 100 (98–111)           | 0.79    |
| Lactate, mmol/L | 1.1 (0.8–1.2) | 1.0 (0.7–1.1)          | 0.12    |
| Hemoglobin, g/dl | 11.3 (10.8–12.2) | 11.2 (10.7–12.2)      | 0.63    |
| mFv, cm/sec | 56.0 (49.7–71.0)  | 55.3 (47.3–62.7)       | 0.13    |
| Pulsatility Index | 0.91 (0.69–1.13) | 0.92 (0.80–1.05)       | 0.41    |
| Mean NPI | 4.6 (4.3–4.7)     | 4.1 (3.2–4.6)          | 0.30    |
| iPbtO22, mmHg | 17 (16–19)    | 22 (20–26)             | <0.01   |
| Brain hypoxia, n (%) | 20 (80)       | 6 (21)                 | <0.01   |

(Tables 1, 2). CPP was progressively increased to 83 (80–86) mmHg and 92 (90–96) mmHg, which resulted in a significant PbtO2 increase [to 22 (19–22) mmHg and 24 (20–24) mmHg, respectively; p < 0.001; Table 2]. During CPP increase, ICP also significantly decreased from baseline values. Median CPP value corresponding to PbtO2 values ≥ 20 mmHg on day 1 was 79 (74–87) mmHg, with 2 (4%) patients who never achieved such target; similar CPP values corresponding to PbtO2 values >20 mmHg were observed in traumatic (n = 38) and non-traumatic brain injury [79 (75–86) mmHg vs. 77 (72–88) mmHg; p = 0.52]. CPP challenges were repeated in 34 patients on day 2, 23 on day 3, 11 on day 4, and 7 on day 5; reasons for not performing CPP challenges the following days were mainly increased ICP (n = 4), the need for CPP > 90 mmHg to keep stable cerebral oxygenation (n = 5), or absence of operator and discontinuation of vasopressor therapy in others. Two patients on day 1 and 1 patient on day 3 never achieved the PbtO2 target. Similar values of CPP corresponding to PbtO2 values ≥ 20 mmHg were observed in the following days [80 (73–87) mmHg on day 2; 79 (72–92) mmHg on day 3; 80 (72–89) mmHg on day 4; 80 (68–92) mmHg on day 5; Figure 1]. No significant complications (i.e., increase in ICP, arrhythmias) during CPP challenge were reported.

Secondary Outcomes
A total of 25 (47%) were PbtO2 responders during the CPP challenge on day 1. PbtO2 responders had similar characteristics to non-responders, including the presence of TBI, with the exception a lower PbtO2 on day 1 and 1 patient on day 3 never achieved the PbtO2 target. Similar values of CPP corresponding to PbtO2 values ≥ 20 mmHg were observed in the following days [80 (73–87) mmHg on day 2; 79 (72–92) mmHg on day 3; 80 (72–89) mmHg on day 4; 80 (68–92) mmHg on day 5; Figure 1]. No significant complications (i.e., increase in ICP, arrhythmias) during CPP challenge were reported.

Outcomes

| | Responder (n = 25) | Non-responder (n = 28) | p-value |
|----------------|--------------------|------------------------|---------|
| ICU stay, days | 15 (12–24)        | 23 (11–33)             | 0.18    |
| Hospital mortality, n (%) | 11 (44)    | 7 (25)                 | 0.16    |
| GOS 3 months | 3 (1–4)           | 3 (1–4)                | 0.37    |
| UO | 16 (64)           | 17 (61)                | 1.00    |

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; RRT, renal replacement therapy; PaCO2, partial arterial CO2 pressure; PaO2, partial arterial oxygen pressure; mFv-MCA, mean MCA flow velocity; NPI, neurological pupil index; iPbtO22, brain tissue oxygenation at baseline; ICU, intensive care unit; GOS, Glasgow Outcome Scale.
A total of 19 (56%), 10 (42%), 4 (36%), and 3 (43%) were PbtO₂ responders during the CPP challenge on days 2, 3, 4, and 5, respectively. A total of 18 (53%), 12 (50%), 4 (36%), and 3 (43%) had baseline brain tissue hypoxia at baseline on days 2, 3, 4, and 5, respectively.

A total of 123 paired assessment of PbtO₂ with mFV and PI changes and 59 of PbtO₂ with NPI changes were available over the first 5 days of assessment. No correlation of PbtO₂ changes were observed with changes in mFV or PI (correlation index of −0.043 and −0.031, with p-values of 0.57 and 0.68, respectively), while a weak correlation between PbtO₂ and NPI changes was observed (correlation index of 0.181, p = 0.017).

Differences between patients with UO and FO are shown in Table 1. Before the CPP challenge, baseline characteristics were similar between groups on day 1. Also, changes in PbtO₂ over time on day 1 were not statistically significant between groups (Table 2; Figure 2).

**DISCUSSION**

In this study, including a heterogeneous population of brain injured patients, increasing CPP resulted in a significant increase of the brain oxygenation in most of patients. The “optimal” CPP, i.e., the CPP value corresponding to the absence of tissue hypoxia, was higher than in recommended targets (i.e., around 80 mmHg).

Half of patients showed a significant increase in PbtO₂ during the CPP challenge, in particular, if they had lower PbtO₂ values at baseline. The effects of CPP on PbtO₂ changes were similar in the following days of assessment. Non-invasive neuromonitoring could not adequately predict PbtO₂ changes during CPP increase.

The improvement in PbtO₂ values during CPP increase using vasopressors has also been reported in previous studies. Johnston et al. reported a significant increase in brain oxygenation when CPP was increased from 70 to 90 mmHg (8); these changes were also associated with an increase in cerebral blood flow and a
increase CPP below the lower limit of autoregulation (i.e., the value of CPP corresponding to the direct dependency of cerebral blood flow from the systemic driving pressure) (19), recommended CPP targets can still result in tissue hypoxia in the absence of elevated ICP, as autoregulation might be impaired or the lower limit shifted toward higher CPP thresholds in brain injured patients (20). Individualized CPP values based on optimal autoregulation status has also been suggested in TBI patients (20); however, targeting “safe” CPP values based on the plateau curve of autoregulation could not correspond to adequate brain oxygenation in some patients (21). In one study (19), PbtO2 was pressure dependent when autoregulation was impaired, while it remained within stable values if autoregulation was intact. However, tissue hypoxia could occur even within normal autoregulation indices (19), thus suggesting that only the presence of PbtO2 monitoring could help to optimize CPP and avoid tissue hypoxia. As such, it is not surprising that changes in PbtO2 during the CPP challenge would not correlate with changes in mFV or PI, two parameters derived from the analysis of cerebral blood flow velocities that are commonly used to estimate cerebral hypoperfusion in the presence of intracranial hypertension (22). In SAH patients, no correlation was observed between PbtO2 measurements and, simultaneously, TCD recording (23). In another study including TBI patients, episode of cerebral hypoxia had all mFV < 40 cm/s; however, no correlation was observed between PbtO2 and mFV in the whole cohort (24). Unfortunately, we did not specifically assess cerebral autoregulation in our study and could not provide additional data to the relationship between autoregulatory status and brain oxygenation. Similarly, NPI assessment using automated pupillometry could reflect elevated ICP (25); however, as tissue hypoxia may occur even within normal ICP values, the lack of sufficient correlation between PbtO2 and NPI changes was expected.

This study has several limitations to acknowledge. First, the small sample size and monocentric and retrospective design might introduce significant selection biases and limit the generalizability of our findings, although characteristics of included and excluded patients were similar. Second, although we suggested the need for higher than recommended CPP targets, MAP transducer was zeroed at the atrium level, while some centers would place the zero-reference point next to cerebral anatomical structures, i.e., the foramen of Monro, which would result in 10–15 mmHg lower CPP, depending on the elevation of the head of the bed (usually 15–30°) (26). Third, many patients had baseline ICP, CPP, and PbtO2 within normal values at baseline, which might not entirely justify a daily “CPP challenge.” However, the duration of CPP challenge was short, being supervised by an experienced intensivist, and was clinically relevant, as conducted in a well-designed approach, and informative for daily patient management. Interestingly, in those patients with normal PbtO2 levels at baseline, lower than recommended CPP targets might have been theoretically used, still maintaining adequate oxygen levels. However, lower CPP values would be outside of routine management in brain injured patients and future studies should prospectively evaluate the safety of such approach. Fourth, the procedure was considered as safe (i.e., no complications were recorded); however, we did not assess changes in cerebral metabolism (i.e., glucose or lactate/pyruvate ratio), which might have also been influenced by changes in brain hemodynamics. Fifth, CPP augmentation was not compared with other interventions able to increase PbtO2 in brain injured patients (i.e., increase in FiO2 and arterial hyperoxia) (27). As such, whether increased CPP rather than,
as an example, increased FiO2 would result in similar effects on brain oxygenation or would have a different safety profile in brain injured patients remains unknown. Sixth, we only assessed short-terms effects of increasing CPP, while persistently high CPP values might be associated with an increased risk of acute respiratory failure, at least in TBI patients, and would not result in better neurological outcome than standard targets (28). Seventh, we defined tissue hypoxia as a PbtO2 < 20 mmHg; ischemic thresholds for PbtO2 have been tested using the association of this value with patients’ outcome; a recent study identified a threshold of 19 mmHg which adequately separated patients with unfavorable and favorable neurological outcome after TBI (29). However, the ischemic threshold might vary among different brain disease and within patients and the presence of concomitant metabolism monitoring (i.e., microdialysis) might be helpful to identify ischemic levels of PbtO2 when they would be associated with low cerebral glucose levels and increased lactate/pyruvate ratio. Eighth, the cerebrovascular pathophysiology among the different types of acute brain injury is different; in particular, SAH patients can develop delayed cerebral ischemia between 4 and 15 days after the injury, whereas cerebral hyperemia and intracranial hypertension may be more common in TBI patients. As such, our findings are also relevant to the very early phase after the injury and in the absence of concomitant intracranial hypertension. Finally, we provided different descriptive analyses without multivariable assessment, as the number of events was limited; however, multiple statistical comparisons exposes to the inflation of false positive tests within dependent datasets.

CONCLUSIONS

In this heterogeneous population of acute brain injured patients, PbtO2 monitoring suggested the need for higher than recommended CPP targets to avoid tissue hypoxia. A higher response in brain oxygenation to the CPP challenge was observed in those patients with low PbtO2 values at baseline. The effects of CPP increase over brain oxygenation are consistent over time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Erasme Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FST, SS, and MK conceived the study protocol. AQ and FST performed the transcranial Doppler. MK, EG, and LP collected the data. HN, LP, and MK analyzed the data. FST, MK, JC, and OD drafted the present manuscript. SS, EG, LP, and AQ critically revised the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.732830/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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