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Stroke

CLINICAL AND POPULATION SCIENCES

Optimal Cerebral Perfusion Pressure and Brain Tissue Oxygen in Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Targeting a cerebral perfusion pressure optimal for cerebral autoregulation (CPPopt) has been gaining more attention to prevent secondary damage after acute neurological injury. Brain tissue oxygenation ($PbtO_2$) can identify insufficient cerebral blood flow and secondary brain injury. Defining the relationship between CPPopt and $PbtO_2$ after aneurysmal subarachnoid hemorrhage may result in (1) mechanistic insights into whether and how CPPopt-based strategies might be beneficial and (2) establishing support for the use of $PbtO_2$ as an adjunctive monitor for adequate or optimal local perfusion.

METHODS: We performed a retrospective analysis of a prospectively collected 2-center dataset of patients with aneurysmal subarachnoid hemorrhage with or without later diagnosis of delayed cerebral ischemia (DCI). CPPopt was calculated as the cerebral perfusion pressure (CPP) value corresponding to the lowest pressure reactivity index (moving correlation coefficient of mean arterial and intracranial pressure). The relationship of (hourly) deltaCPP (CPP—CPPopt) and $PbtO_2$ was investigated using natural spline regression analysis. Data after DCI diagnosis were excluded. Brain tissue hypoxia was defined as $PbtO_2$ <20 mmHg.

RESULTS: One hundred thirty-one patients were included with a median of 44.0 (interquartile range, 20.8–78.3) hourly CPPopt/PbtO2 datapoints. The regression plot revealed a nonlinear relationship between $PbtO_2$ and deltaCPP (P<0.001) with $PbtO_2$ decrease with deltaCPP <0 mmHg and stable $PbtO_2$ with deltaCPP ≥0mmHg, although there was substantial individual variation. Brain tissue hypoxia (34.6% of all measurements) was more frequent with deltaCPP <0 mmHg. These dynamics were similar in patients with or without DCI.

CONCLUSIONS: We found a nonlinear relationship between $PbtO_2$ and deviation of patients' CPP from CPPopt in aneurysmal subarachnoid hemorrhage patients in the pre-DCI period. CPP values below calculated CPPopt were associated with lower $PbtO_2$. Nevertheless, the nature of $PbtO_2$ measurements is complex, and the variability is high. Combined multimodality monitoring with CPP/CPPopt and $PbtO_2$ should be recommended to redefine individual pressure targets (CPP/CPPopt) and retain the option to detect local perfusion deficits during DCI ($PbtO_2$), which cannot be fulfilled by both measurements interchangeably.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: brain ■ brain injuries, traumatic ■ hyperemia ■ infarction ■ partial pressure

Functional cerebral autoregulation is paramount to compensate for the pathological cascades occurring after aneurysmal subarachnoid hemorrhage (aSAH). Impairment of cerebral autoregulation typically precedes delayed cerebral ischemia (DCI) in patients with aSAH[1–3] and information on autoregulation may be used to predict DCI.[4] It is yet unclear whether it can be used to direct therapy. Optimal cerebral perfusion

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Nonstandard Abbreviations and Acronyms

ABP	arterial blood pressure
aSAH	aneurysmal subarachnoid hemorrhage
CBF	cerebral blood flow
CPP	cerebral perfusion pressure
CPPopt	optimal cerebral perfusion pressure
CT	computed tomography
CUIMC	Columbia University Irving Medical Center
DCI	delayed cerebral ischemia
HIMALAIA	Hypertension Induction in the Management of Aneurysmal Subarachnioid Hemorrhage With Secondary Ischemia
ICP	intracranial pressure
$PbtO_2$	brain tissue oxygenation
PRx	pressure reactivity index

pressure (CPPopt) is the value of cerebral perfusion pressure (CPP) at which autoregulation is the best.[5–8] In studies on patients with traumatic brain injury (TBI), from where the concept of CPPopt was derived, the difference of CPP and CPPopt (deltaCPP) is an even better predictor of outcome than deviation from a universal guideline-driven CPP target range.[8] Targeting CPPopt may also be beneficial in patients with aSAH to improve autoregulation and avoid both episodes of too low (hypoperfusion) and too high (hyperemia) cerebral blood flow (CBF). However, basic clinical research on the utility of CPPopt in aSAH is scarce.

Monitoring for complications such as DCI in comatose patients with aSAH is currently based on several options of neuromonitoring, including the invasive measurement of partial pressure of brain tissue oxygenation ($PbtO_2$). Measuring $PbtO_2$ is recommended in the current consensus statement for multimodality neuromonitoring, and its implementation has been associated with improved clinical outcomes.[9–11] Episodes with poor oxygenation can be associated with complications such as cerebral ischemia/infarction, breakdown of cellular metabolism, worsening of neurological outcome.[12,13] The relationship of CPPopt and $PbtO_2$ has not been documented to date. Characterizing their interplay is interesting to better understand the impact of deviations from CPPopt on cerebral physiology and, in turn, the potential benefit of CPPopt based management strategies. We hypothesized that $PbtO_2$ correlates with the deviation from CPPopt, with (1) the lowest $PbtO_2$ values (focal cerebral hypoxia) with large negative deviation, (2) higher $PbtO_2$ values with actual CPP close to CPPopt, and (3) the highest $PbtO_2$ values (focal cerebral hyperoxia) with large positive deviation, in correspondence to the suspected autoregulation curve. This relationship may differ between patients with and without DCI. In patients with DCI, where autoregulation is expected to be worse than in patients without DCI,[2] $PbtO_2$ may react more strongly to deviations from CPPopt.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Two patient cohorts were combined (NewYork–Presbyterian Hospital–Columbia University Irving Medical Center [CUIMC], from 2007 to 2021[14] and Rheinisch-Westfälische Technische Hochschule Aachen [AU], Germany, from 2014 to 2021). Data collection for the prospective Subarachnoid Hemorrhage Outcomes Project at CUIMC has been described previously.[14] Relevant data on demography, clinical course, and high-frequency vital signs from patients at AU were included into a prospective databank, including scheduled follow-up visits or telephone assessments of clinical outcome at 3, 6, and 12 months after discharge.[15] Prospective data collection was approved by institutional review boards in both centers and informed consent was given by all patients or their representatives before study inclusion. Patients with nonaneurysmal SAH, arteriovenous malformation-associated aneurysms, and patients <18 years of age were excluded. All patients with at least 12 hours of corresponding $PbtO_2$ and CPPopt measurements were included in analysis. The study was reported according to the STROBE criteria (Supplemental Material).[16]

Treatment Algorithm

Treatment followed the American Heart Association guidelines[17] at CUIMC, while AU followed the European Stroke Organization guidelines,[18] without major differences in standard operating procedures. All patients were treated in neurological or neurosurgical intensive care units. Patients with Hunt and Hess grades 3 to 5 and Glasgow Coma Scale score <8 at CUIMC and patients with Hunt and Hess grades 3 to 5 or modified Fisher scale score 3 to 4 at AU were considered at high risk for DCI and received invasive neuromonitoring, unless early mortality was anticipated. At CUIMC, separate intracranial pressure (ICP) and $PbtO_2$ probes (ICP: Camino System, Integra Neurosciences, Plainsboro, NJ, $PbtO_2$: Licox, Integra, Plainsboro, NJ) were placed according to a previously published institutional protocol,[19] while in patients at AU, a combined ICP-$PbtO_2$-probe was placed (Neurovent PTO, Raumedic, Helmbrechts, Germany). Probes were placed unilaterally into the watershed zone between anterior and middle cerebral artery territories in the frontal lobe expected to be affected most (side of aneurysm or dominant blood distribution) or on the right side for midline aneurysms and symmetrical blood distribution. Monitoring was aligned to recommendations from the Neurocritical Care Society and the European Society of Intensive Care Medicine, and local guidelines.[9,20,21] All patients received arterial lines zeroed at the phlebostatic axis for arterial blood pressure (ABP) monitoring. Digital physiologic data were from General Electric Solar 8000i monitors

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(Milwaukee, WI) and acquired at a sampling frequency of 240 Hz using data acquisition system (CUIMC: BedmasterEX [Excel Medical Electronics, Jupiter, FL], AU: Moberg Component Neuromonitoring Systems [Moberg Research, Inc, Ambler, PA]). From 2012 until 2021 at CUIMC, digital physiologic data were from Philips Intellivue monitors (Amsterdam, the Netherlands) and acquired at a sampling frequency of 125 Hz using data acquisition systems (BedmasterEX from 2012 until 2014, ICM+ [Cambridge Enterprise, United Kingdom] from 2014 until 2019, Philips Data Warehouse Connect from 2019 until 2021).

Outcome Definition

The goal of the study was to assess the relationship between $PbtO_2$ and deltaCPP, which was additionally split between patients with and without DCI. Brain tissue hypoxia (BTH) was defined as hourly measurements with $PbtO_2$ <20 mmHg. DCI was defined in both centers as a ≥2-point change in Glasgow Coma Scale or new focal neurological deficit lasting for >1 hour and not associated with surgical treatment, or a new cerebral infarct on brain imaging that is not attributable to any other causes.[17] AU additionally defined a territorial or watershed deficit on computed tomography (CT) perfusion as DCI. CT perfusion was conducted when triggered by a worsening in neuromonitoring results or at individual elective time points in comatose patients. The large window for DCI onset or presentation makes direct comparison across patients over time challenging. To address this, we used the day of bleed as the temporal anchor to align the monitoring data and removed the data post-DCI diagnosis to compare the physiologic monitoring values of 2 outcomes while avoiding potential influences of DCI treatment on the physiology. To avoid unbalanced or disparate data time frames of patients with and without DCI, data of patients without DCI were included only until the mean time of DCI diagnosis (ie, until day 7).

Data Processing and Analysis

The following baseline characteristics and grading scales were prospectively recorded at admission: age, sex, history of hypertension, Hunt and Hess grades, and modified Fisher scale. Clinical outcome was assessed 6 months after discharge using the modified Rankin Scale via in-person and/or telephone interviews. Artifact-free segments of $PbtO_2$, ABP, and ICP data were manually identified at the 2 centers. The immediate time period following $PbtO_2$ probe placement up until completed calibration was evaluated by 2 reviewers independently from each other, and excluded from analysis. Later, artifacts were noted to typically result from patient monitor disconnections for nursing care, malfunctioning equipment, or transport off the unit.

Calculation of Measures of Autoregulation

Cerebrovascular pressure reactivity was calculated using the pressure reactivity index (PRx).[6,22] ICP and ABP were time-averaged over 10-second intervals. The PRx was then computed as a Pearson correlation coefficient calculated over a 5-minute moving window (with 80% overlap) between slow changes in ICP and spontaneous fluctuations in ABP.[5,22] The CPP value at which the lowest value of PRx is experienced in a period of time is considered the optimal CPP (CPPopt).[5] To calculate CPPopt, 5-minute median CPP values were divided into 16 bins spanning 5 mmHg. A parabolic curve was applied and the CPP bin with the lowest PRx value was recorded as the CPPopt. This value was updated every minute and trended based on a moving 4-hour window. A threshold of 50% was set in order to generate a curve to calculate CPPopt (>50% PRx values within time window must be present). DeltaCPP was calculated as the patients' actual CPP minus CPPopt every minute.

Statistical Analysis

We plotted $PbtO_2$, CPP, PRx, and BTH over binned deltaCPP for all patients and patients with and without diagnosis of DCI in follow-up (Figure [B] through [D]). Because of the nonlinear relationship between $PbtO_2$ and deltaCPP, we modeled this relationship using nonlinear regression using natural splines (Figure [A]).[23] For this, we used the generalized linear model and fit the natural splines using python statsmodel library.[24] Wilcoxon rank sum test was used for comparing continuous variable and χ^2 test was used for comparing categorical variables. Statistical significance was assumed at $P<0.05$. Data processing and analysis were performed using MATLAB (MATLAB and Statistics Toolbox Release 2015a, The Mathworks, Inc, Natick, MA), Python (Python Software Foundation, https://www.python.org/), and ICM+ (Cambridge Enterprise, Cambridge, United Kingdom).

RESULTS

There were 1233 (CUIMC: n=990; AU: n=243) patients with aSAH of which 265 (CUIMC: n=140; AU: n=125) had continuous neuromonitoring data available. One hundred thirty-one patients (CUIMC: n=52, AU: n=79) fit the inclusion criteria (n=134 excluded without data before DCI before day 7 (mean time of DCI occurrence) or with <12 combined CPPopt/ $PbtO_2$ datapoints). The median age was 54 (IQR, 46.5–64.0) years, n=94 (71.8%) female, median Hunt and Hess grades 4 (IQR, 3–5) and median modified Fisher scale score 3 (IQR, 2–4; Table 1). DCI was diagnosed in n=64 (48.9%) patients with invasive neuromonitoring in total, with n=16 (30.8%) patients at CUIMC and n=48 (60.8%) patients at AU. DCI was diagnosed 7.2±3.3 days after hemorrhage. In 26 of 45 (57.8%) patients in the AU cohort who were diagnosed with DCI via CT perfusion, the ICP-$PbtO_2$-probe was located within the hypoperfused territory at time of DCI diagnosis, according to previously established cut-offs.[25] Age and modified Fisher scale were significantly different ($P<0.05$) between patients with and without DCI (Table 1). There were no statistical differences in physiological data values between patients with and without DCI (Table 2). Out of 16.614 hours of physiological data, both deltaCPP and $PbtO_2$ were present simulateously in 7806 (47.0%) hours, of which 4449 (57.0%) hours were recorded within the first 7 days after hemorrhage and included for analysis (44.0 [20.6–78.3] per patient).

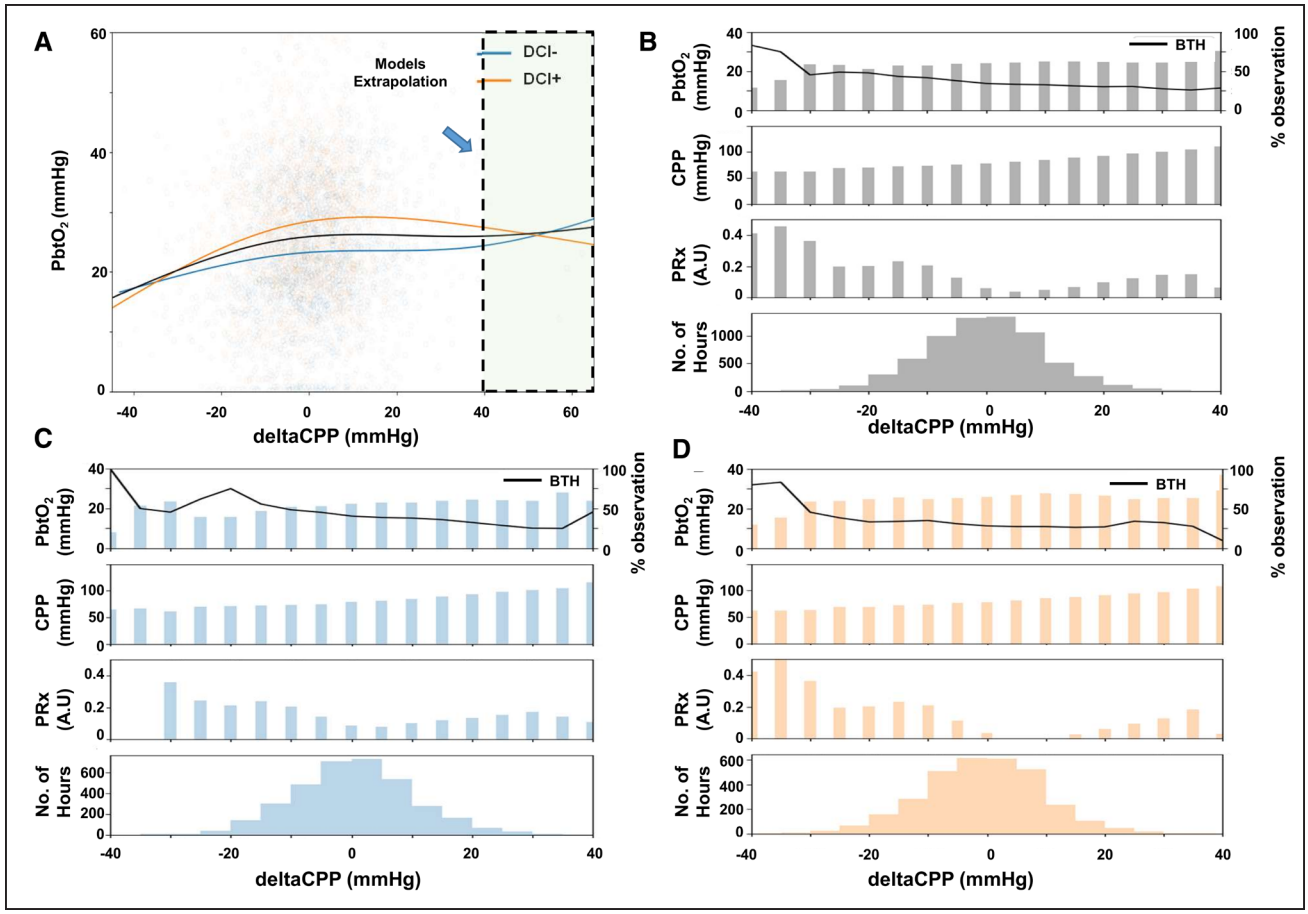

Figure. The relationship between $PbtO_2$ and deltaCPP.
A, Natural spline regression analysis of hourly deltaCPP and $PbtO_2$ pairs. **B**, $PbtO_2$, cerebral perfusion pressure (CPP), pressure reactivity index (PRx) values, and data availability separated by 5 mmHg deltaCPP bins. Black line indicates the proportion of brain tissue hypoxia (BTH) from all measurements within a bin. **C** and **D**, Data separated by patients without delayed cerebral ischemia (DCI; **C**) or with (**D**) DCI.

Median CPPopt was 81.8 (76.8–90.5) mmHg, and median $PbtO_2$ was 23.6 (18.7–31.8) mmHg. Spline regression demonstrated that there was a nonlinear relationship between $PbtO_2$ and deltaCPP (P<0.001; Table S1). Visual inspection of the regression plot (Figure [A]) showed that the curve may be divided into (at least) 2 segments, with increase of $PbtO_2$ with increase of deltaCPP until deltaCPP approximates 0 mmHg and with relatively stable $PbtO_2$ values with deltaCPP ≥0 mmHg. This dynamic was observed regardless of the occurrence of DCI later on. $PbtO_2$ with deltaCPP <0 mmHg (23.6 [16.5–32.7] mmHg) was significantly different to deltaCPP ≥0 mmHg (25.0 [17.9–33.84] mmHg, P<0.001). Mean PRx was significantly higher with deltaCPP <0 mmHg (0.11 [−0.09 to 0.33]) than with ≥0 mmHg (0.06 [−0.13 to 0.26]; P<0.0001).

BTH ($PbtO_2$ <20 mmHg) was noted in n=1542 (34.7%) measurements in total. Of these, n=843 (54.7%) and n=699 (45.3%) were observed with deltaCPP <0 or ≥0 mmHg, respectively. When separating the proportion of BTH by 5 mmHg deltaCPP bins, BTH episodes were more frequent with decreasing deltaCPP (Figure [B]).

DISCUSSION

Cerebral autoregulation has historically been described as a triphasic relationship (Lassen's curve), in which CBF is maintained stable between certain blood pressure limits, but this concept has been challenged recently.[26,27] A quadriphasic theory of autoregulation was recently proposed by Klein et al[27] from experimental data, who documented 2 upper limits of autoregulation, owing to the separate reactions of smaller and larger arterioles. Our hypothesis was that the reaction of cohort $PbtO_2$ could delinate the functionality of autoregulation. Our results support a nonlinear relationship between $PbtO_2$ and the deviation of actual patients' CPP from CPPopt (deltaCPP) in patients with aSAH. However, mainly 2 phases can be observed in our data: $PbtO_2$ seems to be most stable when CPP is close to or above CPPopt, while CPP below CPPopt corresponds to decreasing $PbtO_2$ values. Mean $PbtO_2$ was slightly but significantly lower with deltaCPP <0 mmHg. With very low deltaCPP (<−30 mmHg), episodes of brain tissue hypoxia become more frequent. Conversely, positive deltaCPP does not lead to further increase of $PbtO_2$. The natural spline regression

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Table 1. Comparison of Patient Characteristics

	n=131	DCI+ n=64	DCI– n=67	*P* value*
Age, median (IQR)	54.0 (46.5 to 64.0)	51.5 (44.0 to 60.0)	59.0 (49.0 to 66.0)	0.008
Female sex, n (%)	94 (71.76)	44 (72.1)	47 (72.3)	0.869
MFS, n (%)				0.047
1	29 (23.02)	11 (17.19)	18 (26.87)	
2	26 (20.63)	9 (14.06)	17 (25.37)	
3	33 (26.19)	17 (26.56)	18 (26.87)	
4	35 (27.78)	26 (40.63)	12 (17.91)	
HH, n (%)				0.589
1	5 (3.82)	3 (4.92)	2 (2.99)	
2	14 (10.69)	8 (13.11)	6 (8.96)	
3	31 (23.66)	13 (21.31)	18 (26.87)	
4	47 (35.88)	25 (40.98)	21 (31.34)	
5	34 (25.95)	12 (19.67)	20 (29.85)	
mRS (3 mo), n (%)				0.075
1	7 (5.34)	5 (7.46)	2 (3.13)	
2	16 (12.21)	10 (14.93)	6 (9.38)	
3	15 (11.45)	10 (14.93)	5 (7.81)	
4	19 (14.5)	6 (8.96)	13 (20.31)	
5	21 (16.03)	7 (10.45)	14 (21.88)	
6	41 (31.3)	23 (34.33)	18 (28.13)	

DCI+ indicates patients with DCI; DCI–, patients without DCI; HH, Hunt and Hess grade; IQR, interquartile range; MFS, modified Fisher Scale; and mRS, modified Rankin Scale.

*Considered significant if $P<0.05$.

model predicts this upward trend for deltaCPP values >+40mmHg. However, deltaCPP values in this range were rarely reached in our cohort, therefore this trend must be interpreted as a purely mathematical extrapolation. A third (or fourth) phase of autoregulation therefore cannot be observed in our data.

A possible explanation is the effort to maintain physiological CPP values in patients (observational study) while experimental settings can actively explore the reaction to more extreme pressure values.[27] A CPP challenge would be necessary to determine individual limits of autoregulation and therefore, the individual range that CPP may deviate from CPPopt before $PbtO_2$ begins to decrease or increase more passively. Overall, the autoregulation curve may be shifted towards higher CPP values in patients with aSAH but with lower total CBF, increasing the chance to encounter hypoxia at lower CPP values and to observe the lower limit of autoregulation in the $PbtO_2$/deltaCPP relationship, but not the upper limit of autoregulation.[25,28,29] Treatment phases with induced hypertension may depict a third phase more clearly, but were excluded from this analysis to avoid iatrogenic influence on CPPopt calculations. In theory, CBF (and $PbtO_2$ to some extent) may increase further during hypertension, if the upper limit of autoregulation is exceeded. This represents the rationale for treating DCI with induced hypertension, for which conflicting data have been reported. Gathier et al. found that the overall

Table 2. Comparison of Physiological Data Within the First 7 Days After Hemorrhage

	All	DCI+	DCI–	
$PbtO_2$	24.12 (18.16 to 32.35)	23.41 (16.64 to 29.6)	24.62 (18.61 to 33.97)	0.325
ABP	92.53 (86.41 to 101.7)	93.99 (86.69 to 104.57)	90.33 (85.87 to 99.02)	0.263
ICP	7.89 (5.88 to 11.26)	8.66 (5.8 to 12.78)	7.61 (6.0 to 9.78)	0.338
CPP	82.69 (75.55 to 94.67)	82.62 (75.36 to 96.93)	83.03 (76.48 to 94.03)	0.680
CPPopt	82.69 (76.97 to 91.99)	81.85 (76.21 to 91.99)	83.73 (78.6 to 91.8)	0.667
deltaCPP	–0.13 (–3.03 to 3.0)	–0.13 (–3.04 to 3.83)	–0.16 (–3.03 to 1.8)	0.474
PRx	0.07 (–0.06 to 0.21)	0.12 (0.0 to 0.24)	0.04 (–0.09 to 0.16)	0.086

ABP indicates arterial blood pressure; CPP, cerebral perfusion pressure; CPPopt, optimal cerebral perfusion pressure; deltaCPP, CPP-CPPopt; DCI+, patients with DCI; DCI–, patients without DCI; ICP, intracranial pressure; and PRx, pressure reactivity index.

CBF in the HIMALAIA trial (Hypertension Induction in the Management of Aneurysmal Subarachnioid Hemorrhage With Secondary Ischemia) did not increase during induced hypertension, but the region of interest with the lowest pre-treatment CBF increased substantially, albeit not significantly (P=0.05).[30,31] In contrast, in a setting with induced hypertension and vasodilation together, we found that a higher pressure target (>180 mmHg systolic) corresponded to even lower $PbtO_2$ values than a lower pressure target (>120 mmHg systolic).[32] As a future prospect, analyzing the relationship of deltaCPP and $PbtO_2$ during phases with induced hypertension may delineate an upper limit of autoregulation, and give insight into the oxygen-plus that can or cannot be expected by hypertensive treatment.

It must also be acknowledged that autoregulation refers to the relationship of perfusion pressure and cerebral flow, for which $PbtO_2$ is only an imperfect surrogate and may therefore not reflect the autoregulation curve entirely. $PbtO_2$ measurements are influenced by other factors beyond insufficient CBF such as oxygen diffusion depending on arterial and venous oxygen tensions, oxygen consumption or capillary blood distribution, which may be severely disturbed after aSAH.[33–37] Furthermore, $PbtO_2$ is a local marker and may be noninformative for distal areas of impaired autoregulation or mismatched perfusion. Regional differences in autoregulation have recently been found in patients with malignant stroke; therefore, it is conceivable that both $PbtO_2$ and CPPopt values (by the current method of calculation) may differ in areas with intact or disturbed autoregulation.[38] These may be reasons that limits of autoregulation could not be detected as clearly in our data. Nevertheless, detecting episodes of brain tissue hypoxia remains interesting as an adjunctive parameter to monitoring of CPP/CPPopt, as it can aid the diagnosis of DCI and estimate the efficacy of DCI treatment.[32] Active measures to improve $PbtO_2$ such as increasing CPP are also under investigation as they may have a positive impact on long-term neurological outcome.[39,40]

Generally poorer autoregulation has been described in patients with DCI versus those without DCI and autoregulation may be used to predict DCI.[41] We hypothesized that patients with DCI could therefore be more strongly dependent on a deltaCPP close to zero to maintain good $PbtO_2$. Our data did not support this hypothesis. The 2-phasic $PbtO_2$ development with increasing deltaCPP was similar between groups. Mean $PbtO_2$ and PRx were comparable during the analyzed time frame. We have recently demonstrated that autoregulation may deteriorate significantly only several hours before DCI, similarly to $PbtO_2$.[25,42] Such short-term differences may not be captured in our comparatively longer data time frame, while comparison of selected time frames around DCI to patients without DCI is difficult as there is no corresponding DCI event to match data to.

The range of CPP values, which is optimal as determined by PRx values has been discussed primarily in TBI patients with ICP monitoring. There is most consensus for a recommendation of maintaining deltaCPP ±5 mmHg which was the target of the COGITATE trial (Feasibility and Safety Trial to Guide Cerebral Perfusion Pressure According to CPPopt Goals in Traumatic Brain Injury).[43] It is not yet proven that CPPopt can be used for this purpose in aSAH. CPPopt may be too blunt a target when regional differences in autoregulation impairment and/or perfusion exist with DCI. Differences between TBI and aSAH may require a different strategy for CPPopt calculation and the resulting management, including a reinvestigation of the ±5 mmHg optimal range around the target in aSAH patients.[44] If interpreting $PbtO_2$ as a surrogate for adequate CBF and considering only $PbtO_2$, our results would suggest that the range for CPPopt may be much wider in aSAH, as decrease of $PbtO_2$ <20 mmHg on cohort level was only observed with deltaCPP <—20 mmHg. However, our data also indicate that hyperperfusion with positive deltaCPP may be tolerated better than hypoperfusion in patients wit aSAH. Besides a progressive decrease of $PbtO_2$ with negative deltaCPP, worsening of PRx values was also more progressive with negative deltaCPP as compared with positive deltaCPP values. The *U*-shaped curve in TBI patients similarly depicts a steeper increase of PRx with deltaCPP below CPPopt than with positive deltaCPP,[8] but the overall CPPopt recommendation in TBI patients is significantly lower and complications from hyperperfusion such as cerebral edema or seizures are feared more quickly in patients with TBI than with aSAH.[43,45] Avoiding negative deltaCPP could be more important than avoiding positive deltaCPP in aSAH, which may have to be considered when a CPPopt target is defined in aSAH patients.

The CPP values that corresponded to low deltaCPP values and hypoxia were not necessarily pathological according to the current empirical recommendation that only defines a treatment floor of CPP >60 to 70 mmHg.[46,47] Thus, if CPPopt is not calculated, many of these CPPs are accepted as normal and not intervened for despite the potential of improving $PbtO_2$.[40] Similar relationships of CPPopt or optimal ABP and $PbtO_2$ were determined in patients with traumatic brain injury and hypoxic-ischemic brain injury.[48,49] As we observed a large variability of absolute $PbtO_2$ values in relation to deltaCPP, we recommend monitoring both CPP/CPPopt and $PbtO_2$, as they give adjunctive information: CPP/CPPopt may help determine an individual pressure target (range or lower limit), while $PbtO_2$ is most valuable to detect hypoperfusion during DCI.

Limitations

The advantage of a larger case number achieved by combining 2 cohorts was weighted against the disadvantage

of potential confounders. We are not aware of major differences in diagnosis and treatment procedures between both centers, but unknown differences cannot be ruled out completely. DCI was defined differently in the 2 centers owing to the limitations of the current DCI definition, which is based primarily on the clinical diagnosis in awake patients.[50] Both centers defined DCI according to Vergouwen et al[51] as clinical deterioration with an additional imaging basis (cerebral infarction at CU; perfusion delay at AU). CT perfusion is frequently used as another basis for DCI diagnosis as most pathomechanisms assumed to be involved in DCI may result in hypoperfusion measurable by CT perfusion. Assessment of brain tissue oxygen relied on local, invasive measurements, which are dependent on type of probe, location, and site of occurrence of DCI. CUIMC used Licox probes while AU placed Raumedic probes, which can be associated with slightly deviating measurements.[52–54] Independent of probe type, potential differences between patients with and without DCI may be diluted by measurements from DCI patients in whom DCI occurred in territories not covered by the probe. Alternative methods of calculating autoregulation by transcranial doppler velocities or near-infrared spectroscopy are under investigation but are not available for our cohort.[55,56] Finally, the detection of autoregulatory thresholds were made on cohort level, which does not vice versa allow conclusions on an individual patient level.

Conclusions

$PbtO_2$ and deltaCPP have a non-linear relationship with CPP close to or above CPPopt associated with stable $PbtO_2$ values while CPP below CPPopt exhibits $PbtO_2$ decrease. Calculating CPPopt may be more informative than CPP alone, as it helps identify these alterations with CPP in normal boundaries. Owing to the high variability and the manifold influences on $PbtO_2$, additional $PbtO_2$ monitoring may yield complementary information to detect hypoxia as part of DCI and guide rescue treatment.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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