Optimal Cerebral Perfusion Pressure During Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

Optimal Cerebral Perfusion Pressure During Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

Miriam Weiss, MD[1]
Walid Albanna, MD[1]
Catharina Conzen, MD[1]
Murad Megjhani, PhD[2,3]
Jeanette Tas, MSc[4,5]
Katharina Seyfried, MD[1]
Nick Kastenholz, cand. med.[1]
Michael Veldeman, MD[1]
Tobias Philip Schmidt, MD, MHBA[1]
Henna Schulze-Steinen, MD[6]
Martin Wiesmann, MD[7]
Hans Clusmann, MD[1]
Soojin Park, MD[2,3]
Marcel Aries, MD[4,5]
Gerrit Alexander Schubert, MD[1]

OBJECTIVES: The recommendation of induced hypertension for delayed cerebral ischemia treatment after aneurysmal subarachnoid hemorrhage has been challenged recently and ideal pressure targets are missing. A new concept advocates an individual cerebral perfusion pressure where cerebral autoregulation functions best to ensure optimal global perfusion. We characterized optimal cerebral perfusion pressure at time of delayed cerebral ischemia and tested the conformity of induced hypertension with this target value.

DESIGN: Retrospective analysis of prospectively collected data.

SETTING: University hospital neurocritical care unit.

PATIENTS: Thirty-nine aneurysmal subarachnoid hemorrhage patients with invasive neuromonitoring (20 with delayed cerebral ischemia, 19 without delayed cerebral ischemia).

INTERVENTIONS: Induced hypertension greater than 180 mm Hg systolic blood pressure.

MEASUREMENTS AND MAIN RESULTS: Changepoint analysis was used to calculate significant changes in cerebral perfusion pressure, optimal cerebral perfusion pressure, and the difference of cerebral perfusion pressure and optimal cerebral perfusion pressure 48 hours before delayed cerebral ischemia diagnosis. Optimal cerebral perfusion pressure increased 30 hours before the onset of delayed cerebral ischemia from 82.8 ± 12.5 to 86.3 ± 11.4 mm Hg ($p < 0.05$). Three hours before delayed cerebral ischemia, a changepoint was also found in the difference of cerebral perfusion pressure and optimal cerebral perfusion pressure (decrease from −0.2 ± 11.2 to −7.7 ± 7.6 mm Hg; $p < 0.05$) with a corresponding increase in pressure reactivity index (0.09 ± 0.33 to 0.19 ± 0.37; $p < 0.05$). Cerebral perfusion pressure at time of delayed cerebral ischemia was lower than in patients without delayed cerebral ischemia in a comparable time frame (cerebral perfusion pressure delayed cerebral ischemia 81.4 ± 8.3 mm Hg, no delayed cerebral ischemia 90.4 ± 10.5 mm Hg; $p < 0.05$). Inducing hypertension resulted in a cerebral perfusion pressure above optimal cerebral perfusion pressure (+12.4 ± 8.3 mm Hg; $p < 0.0001$). Treatment response (improvement of delayed cerebral ischemia: induced hypertension$^+$ [$n = 15$] or progression of delayed cerebral ischemia: induced hypertension$^-$ [$n = 5$]) did not correlate to either absolute values of cerebral perfusion pressure or optimal cerebral perfusion pressure, nor the resulting difference (cerebral perfusion pressure [$p = 0.69$]; optimal cerebral perfusion pressure [$p = 0.97$]; and the difference of cerebral perfusion pressure and optimal cerebral perfusion pressure [$p = 0.51$]).

CONCLUSIONS: At the time of delayed cerebral ischemia occurrence, there is a significant discrepancy between cerebral perfusion pressure and optimal cerebral perfusion pressure with worsening of autoregulation, implying inadequate but identifiable individual perfusion. Standardized induction of hypertension resulted in cerebral perfusion pressures that exceeded individual optimal cerebral perfusion pressure in delayed cerebral ischemia patients. The potential benefit of individual

DOI: 10.1097/CCM.0000000000005396

blood pressure management guided by autoregulation-based optimal cerebral perfusion pressure should be explored in future intervention studies.

KEY WORDS: brain ischemia; cerebrovascular circulation; critical care; subarachnoid hemorrhage

Poor clinical status after aneurysmal subarachnoid hemorrhage (aSAH) may be further aggravated by delayed cerebral ischemia (DCI) (1). This phenomenon comprises several deleterious processes leading to breakdown of normal cellular functions (2). In this particularly vulnerable phase, the appropriate adjustment of vessel tone to fluctuations of blood pressure and local energy demand (cerebral autoregulation) is important to avoid further mismatch. Cerebral autoregulation is disturbed during DCI, promoting cerebral infarction and poor clinical outcome (3, 4). Although this correlation is well known, autoregulation is not usually integrated into diagnostic algorithms for DCI as there are no established means for intervention.

In traumatic brain injury, functionality of autoregulation varies according to the current level of cerebral perfusion pressure (CPP) (5). From this observation, the concept of an optimal CPP (CPP_{opt}) was derived (6). In essence, CPP_{opt} is a constantly updated CPP value at which cerebral autoregulation is observed to function best. Deviation from this patient- and time-varying value has been linked to poor clinical outcome in traumatic brain injury and, in initial investigations, also in subarachnoid hemorrhage (7, 8). Blood pressure management is typically liberal after the ruptured aneurysm is secured, allowing for intrinsic blood pressure regulation with only a lower safety limit to avoid hypotension (9). This may result in divergence of CPP and CPP_{opt}, particularly during DCI where local hypoperfusion is frequently observed in imaging (10, 11).

The vast majority of treatment regimens for DCI include some form of induced hypertension (iHTN) that is recommended in the American guidelines (12, 13). The European guidelines warn against the potential risks that are referable to not knowing the individual upper limits of perfusion (including edema, hemorrhagic transformation of infarct, reversible leukoencephalopathy, and cardiac adverse effects) (9). Due to the lack of robust evidence around iHTN, the controversy surrounding its benefit persists and has been sparked anew with the results from the randomized controlled Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA (HIMALAIA) trial that yielded inconclusive results (14). Implementing autoregulation-guided, individualized perfusion management (CPP_{opt}) may prove beneficial in the context of DCI. We hypothesized that discrepancies of (spontaneous or induced) CPP from CPP_{opt} contribute to the occurrence of DCI, and we investigated whether these parameters are associated with treatment response from uniformly applied iHTN.

MATERIALS AND METHODS

We prospectively enrolled patients with aSAH greater than or equal to 18 years at a single tertiary care institution from May 2014 to September 2020 (**Fig. 1**) into an institutional databank. Patients without invasive neuromonitoring were not included for analysis. Patients without DCI with neuromonitoring data at day 7 (matched to the mean time of DCI occurrence in the DCI group) served as a control group. All data were collected prospectively except CPP_{opt} that was recalculated at the end of the inclusion period due to the availability of an updated calculation method (15). Consent for inclusion was obtained by patients or their representatives. The data collection was approved by the local ethics committee (EK 062/14). Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guideline for observational studies (16).

Standard Operating Procedure

Monitoring Protocol. Our standard operating procedure for DCI monitoring and management has been detailed previously (17, 18). All awake patients are monitored for DCI clinically. In nonassessable or awake patients with high risk of DCI (Hunt and Hess grade ≥ 3 or grade 1–2 with modified Fisher grade ≥ 3, unless early mortality is anticipated), monitoring is augmented by invasive, multimodal neuromonitoring (intracranial pressure [ICP], brain tissue oxygen [$p_{ti}o_2$], microdialysis; Neurovent PTO, Raumedic, Helmbrechts, Germany). Minimal CPP threshold is greater than 60 mm Hg after aneurysm occlusion, with arterial blood pressure zeroed at heart level.

Delayed Cerebral Ischemia. The decision to classify and treat DCI is based on interdisciplinary consensus between the treating neurosurgical, neuroradiological,

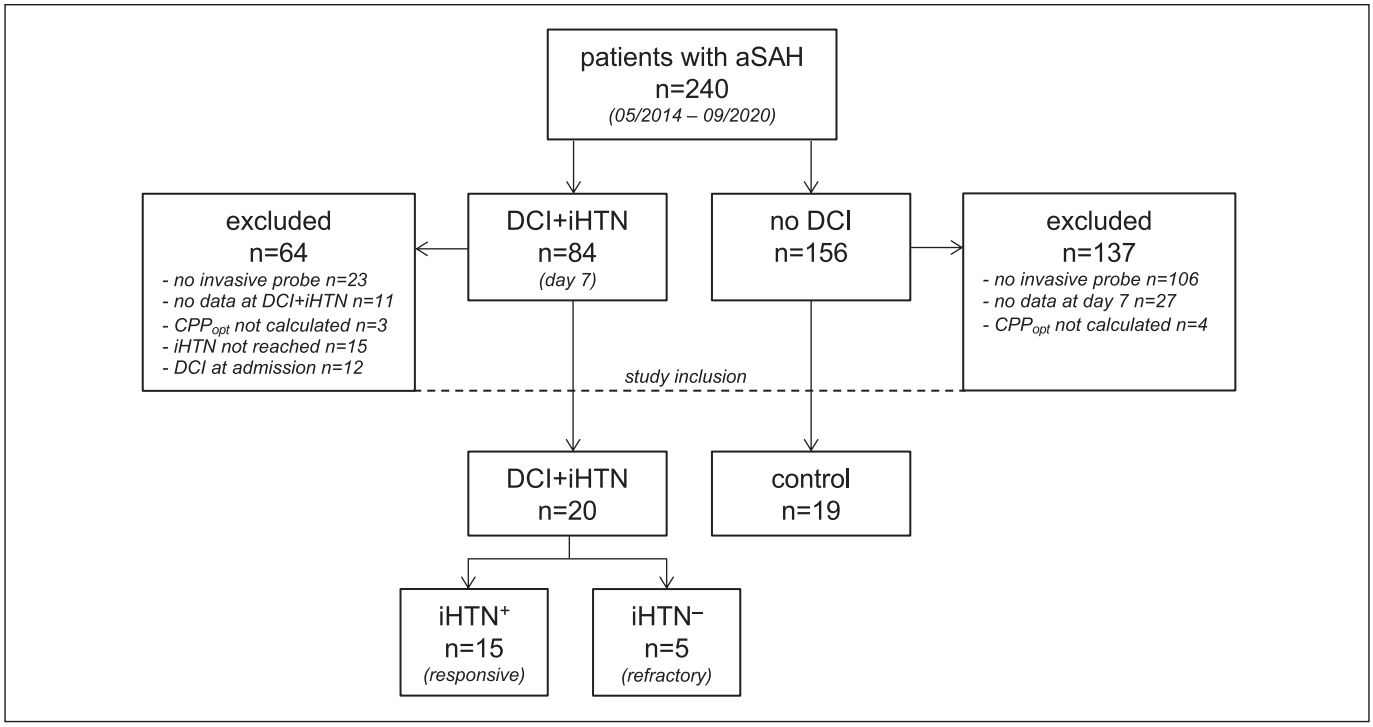

Figure 1. Flow chart of study enrollment and subgroups. aSAH = aneurysmal subarachnoid hemorrhage, CPP_{opt} = optimal cerebral perfusion pressure, DCI = delayed cerebral ischemia, iHTN = induced hypertension.

and neurointensive care physicians. New neurologic impairment or decrease in Glasgow Coma Scale of greater than or equal to 2 for greater than 1 hour unrelated to other causes establishes the clinical diagnosis of DCI in conscious patients (19). Worsening of transcranial Doppler measurements, $p_{ti}O_2$ or lactate/pyruvate ratio is considered a warning sign of DCI, triggering CT perfusion (CTP) imaging to confirm DCI in case of characteristic territorial or watershed hypoperfusion (20, 21). Minimum CTP thresholds for DCI in this cohort were time to drain greater than 10 seconds and mean transit time greater than 6.7 seconds, while minor hypoperfusion is excluded from DCI diagnosis and treatment.

Induced Hypertension. iHTN is introduced via continuous central venous infusion of noradrenaline to achieve a standardized systolic blood pressure target greater than 180 mm Hg. Additional measures include optional RBC transfusion (hemoglobin target > 10 g/dL) and fluid optimization toward normovolemia (12). Response to treatment is closely monitored via neurologic examination in conscious patients, by neuromonitoring parameters and timely repetition of CTP. In patients with DCI and spontaneous hypertension greater than 180 mm Hg, pressure is not raised further and the second stage of rescue treatment is considered.

Endovascular Rescue Treatment. Lack of timely improvement triggers urgent cerebral angiography to consider endovascular rescue treatment (balloon angioplasty or continuous intra-arterial nimodipine) if significant proximal or distal vasoconstriction and perfusion delay is detected.

Analysis Parameters

Waveform data at 100 samples per second (ICP, mean arterial pressure [MAP], CPP) logged by the Raumedic probe were acquired using the MPR2 logO Datalogger and Datalogger software (Raumedic) or, after July 2018, with the Moberg CNS monitor (Component Neuromonitoring System; Moberg Research, Ambler, PA). ICM+ software (University of Cambridge, Cambridge Enterprise, Cambridge, United Kingdom) was used to automate artifact removal and calculate extended parameters (15, 22). This included the pressure reactivity index (PR_x) for cerebral autoregulation measured as a moving Pearson correlation coefficient between MAP and ICP. PR_x is calculated for a 5-minute data frame consisting of 30 10 seconds means of MAP and ICP. PR_x less than 0.2 is considered normal, while values greater than or equal to 0.2 may indicate disturbed autoregulation (23). Finally, PR_x was used to calculate

CPP_{opt} according to the protocol used in the CPP_{opt} Guided Therapy: Assessment of Target Effectiveness (COGiTATE) trial (22). In brief, using a maximally 8-hour long data time frame, 5-minute medians of CPP were allocated into 5 mm Hg bins (*x*-axis) and corresponding PR_x. A best-fit automated U-shaped curve was generated, with the nadir indicating the CPP_{opt} at which PR_x was minimal in that data time frame. The CPP_{opt} value was updated every minute. ΔCPP was calculated as the difference of CPP and CPP_{opt}.

Study Design

The development of all parameters (MAP, ICP, CPP, CPP_{opt}, ΔCPP, and PR_x) was plotted for 48 hours before DCI diagnosis. We used changepoint analysis to identify significant changes in this period leading up to DCI (24). To characterize parameters immediately before DCI, a mean of all parameters was calculated for a 3-hour baseline prior to DCI diagnosis. This baseline was compared with values from the no DCI group matched to the mean time of DCI occurrence in the DCI group (=day 7 after hemorrhage, incorporating all data from this day [24 hr] to account for natural fluctuations).

Mean CPP was calculated for the first 3 hours of iHTN and compared with the 3-hour baseline CPP_{opt} (ΔCPP_{iHTN}) to evaluate how well a target greater than 180 mm Hg is conform to CPP_{opt} at time of DCI. Patients were further dichotomized according to their response to iHTN to characterize whether treatment response is associated with how well CPP_{opt} is met:

1) refractory patients ($iHTN^-$): Patients without reversal of DCI (no improvement of neurologic symptoms and/or persistent hypoperfusion on CTP), requiring endovascular rescue treatment within 24 hours.
2) responsive patients ($iHTN^+$): Patients with reversal of DCI symptoms.

Statistical Analysis

Statistical tests were conducted with IBM SPSS Statistics 26 (SPSS, Chicago, IL) and R Version 4.1.0 (R Core Team [2021]. R: A language and environment for statistical computing. R foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Graphical elements were created with GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Categorical parameters were compared with Fisher exact test. Comparisons between the DCI and no DCI groups were made using Mann-Whitney *U* test after normality testing with the Kolmogorov-Smirnov test. Paired comparisons were made using paired *t* test or Wilcoxon rank-sum test as appropriate. Statistical significance was defined as two-sided *p* value of less than 0.05.

RESULTS

In all patients from the databank with any ICP/MAP monitoring ($n = 110$), using the multiwindow CPP_{opt} calculation resulted in 81.0% ± 17.8% of CPP_{opt} calculated. A total of 20 patients with DCI were included for analysis (Fig. 1). The diagnosis of DCI was established clinically in two patients (10.0%) by a combination of clinical symptoms and CTP deficits in $n = 3$ patients (15.0%) or in $n = 15$ (75.0%) analgosedated patients based on CTP alone. Nineteen patients with neuromonitoring in place did not develop DCI (no DCI group) with comparable baseline demographics except for higher age (**Table 1**).

Changes Before DCI

A significant changepoint of CPP_{opt} occurred 30 hours before onset of DCI, with increase from 82.8 ± 12.5 to 86.3 ± 11.4 mm Hg ($p < 0.05$) (**Fig. 2**). CPP_{opt} was 89.1 ± 8.1 mm Hg 3 hours before DCI. Three hours before DCI, a changepoint was found in ΔCPP (–0.2 ± 11.2 to –7.7 ± 7.6 mm Hg; $p < 0.05$) with a corresponding increase in PR_X (0.09 ± 0.33 to 0.19 ± 0.37; $p < 0.05$) 7 hours prior to DCI, illustrating deteriorating autoregulation. Inspection of the CPP and MAP curves identified a decrease in the 3 hours prior to DCI (CPP 84.0 ± 14.0 to 77.0 ± 10.0 mm Hg, MAP 93.5 ± 14.0 to 88.1 ± 11.7 mm Hg) but these were not found as significant changepoints. ICP before DCI was stable (9.6 ± 6.8 to 9.1 ± 4.2 mm Hg; p = not significant).

When comparing patients with and without DCI, calculated CPP_{opt} was comparable (CPP_{opt} DCI 89.1 ± 8.1 mm Hg, no DCI 89.3 ± 8.3 mm Hg; $p = 0.79$) and autoregulation was also close to the suggested pathologic threshold (PR_x DCI 0.18 ± 0.23, no DCI 0.15 ± 0.19; $p = 0.60$). At time of DCI, CPP was significantly lower in patients with DCI (CPP DCI 81.4 ± 8.3 mm Hg, no DCI 90.4 ± 10.5 mm Hg; $p < 0.05$), resulting

TABLE 1.
Overview of Baseline Characteristics and Treatment Details in All Patients With Induced Hypertension and After Stratification According to Treatment Response

Parameter	DCI			No DCI	*p* DCI Cohort vs No DCI	*p* iHTN⁻ vs iHTN⁺
	Total	iHTN⁻	iHTN⁺			
n (%)	20	5	15	19		
Age (yr)	55.0 ± 14.8	60.4 ± 16.6	53.1 ± 14.3	64.7 ± 10.0	**0.011**	0.221
Female sex, *n* (%)	12 (60.0)	4 (80.0)	8 (53.3)	15 (78.9)	0.301	0.603
Body mass index (kg/m²)	28.1 ± 5.0	26.6 ± 1.4	28.5 ± 5.7	27.9 ± 5.8	0.663	0.457
Hypertension, *n* (%)	10 (50.0)	2 (40.0)	8 (53.5)	9 (47.5)	1.000	1.000
Smoking, *n* (%)	6 (30.0)	2 (40.0)	4 (26.7)	4 (21.1)	0.716	0.613
Hunt and Hess 4–5, *n* (%)	8 (40.0)	1 (20.0)	7 (46.7)	7 (36.8)	1.000	0.603
Modified Fisher 3–4, *n* (%)	16 (80.0)	4 (80.0)	12 (80.0)	10 (52.6)	0.096	1.000
Anterior circulation aneurysm, *n* (%)	18 (90.0)	5 (100)	13 (86.7)	12 (63.2)	0.065	1.000
Clipping, *n* (%)	6 (30.0)	2 (40.0)	4 (26.7)	7 (36.8)	0.741	0.613
Endovascular, *n* (%)	14 (70.0)	3 (60.0)	11 (73.3)	12 (63.2)		
Time to iHTN (d)	6.5 ± 3.1	7.2 ± 1.9	6.3 ± 3.4	–	–	0.358
Total duration of iHTN (d)	12.7 ± 5.2	14.4 ± 5.1	12.1 ± 5.2	–	–	0.407
DCI-related cerebral infarction, *n* (%)	7 (35.0)	2 (40.0)	5 (33.3)	–	–	1.000
Glasgow Outcome Scale 4–5, *n* (%)	7 (36.8)	3 (60.0)	4 (28.6)	10 (52.6)	0.335	0.280

DCI = delayed cerebral ischemia, iHTN = induced hypertension.
Glasgow Outcome Scale 3 mo after discharge (follow-up lost for one patient).
Boldface value indicates significance. Dashes indicate the parameters time to iHTN, total duration of iHTN, and DCI related infarction do not exist for the No DCI group as they are specific to patients with DCI.

in a significant difference in ΔCPP (ΔCPP DCI –7.7 ± 7.6 mm Hg, no DCI +1.3 ± 5.4 mm Hg; $p < 0.01$). This was due to a significantly lower MAP (MAP DCI 88.1 ± 11.7 mm Hg, no DCI 100.1 ± 11.1 mm Hg; $p = 0.01$), whereas no difference was found in ICP (ICP DCI 9.1 ± 4.2 mm Hg, no DCI 9.8 ± 5.8 mm Hg; $p = 0.32$).

Follow-Up Analysis

We conducted a follow-up analysis to identify reasons for negative ΔCPP before DCI. Noradrenaline demand was comparable (DCI 0.09 ± 0.08 vs no DCI 0.07 ± 0.08 μg/kg/min; $p = 0.37$). There were also no differences in hemoglobin (DCI 10.1 ± 1.2 g/dL, no DCI 10.0 ± 1.7 g/dL; $p = 0.53$), the proportion of patients under analgosedation (at least one of propofol, midazolam, or ketamine with an opioid analgesic; DCI $n = 15$ [75%], no DCI $n = 11$ [57.9%]; $p = 0.32$) or whether patients received full dose of oral nimodipine (360 mg/d) or less (≤ 180 mg/d) (DCI full dose $n = 11$ [55.0%], no DCI $n = 12$ [63.2%]; $p = 0.75$). However, patients with DCI received antibiotic treatment significantly more often or were currently sampled for infection due to fever and/or increasing laboratory markers (DCI $n = 19$ [95.0%], no DCI $n = 9$ [47.4%]; $p < 0.01$). There was a nonsignificant trend for a lower overall fluid balance (since admission, without adjustment for transpiration) in DCI patients (DCI –498.9 ± 1,757.5 mL, no DCI 836.5 ± 2,654.8 mL; $p = 0.06$). Fluid balance on the day of DCI was comparable (DCI –16.9 ± 636.7 mL, no DCI 118.5 ± 554.1 mL; $p = 0.51$).

Induced CPP Versus CPP_{opt}

With iHTN, CPP increased significantly (81.4 ± 8.3 mm Hg to 99.4 ± 11.5 mm Hg; $p < 0.0001$). Induced CPP exceeded baseline CPP_{opt} at time of DCI by +12.4 ± 8.3 mm Hg (ΔCPP_{iHTN}; $p < 0.0001$) (**Fig. 3**).

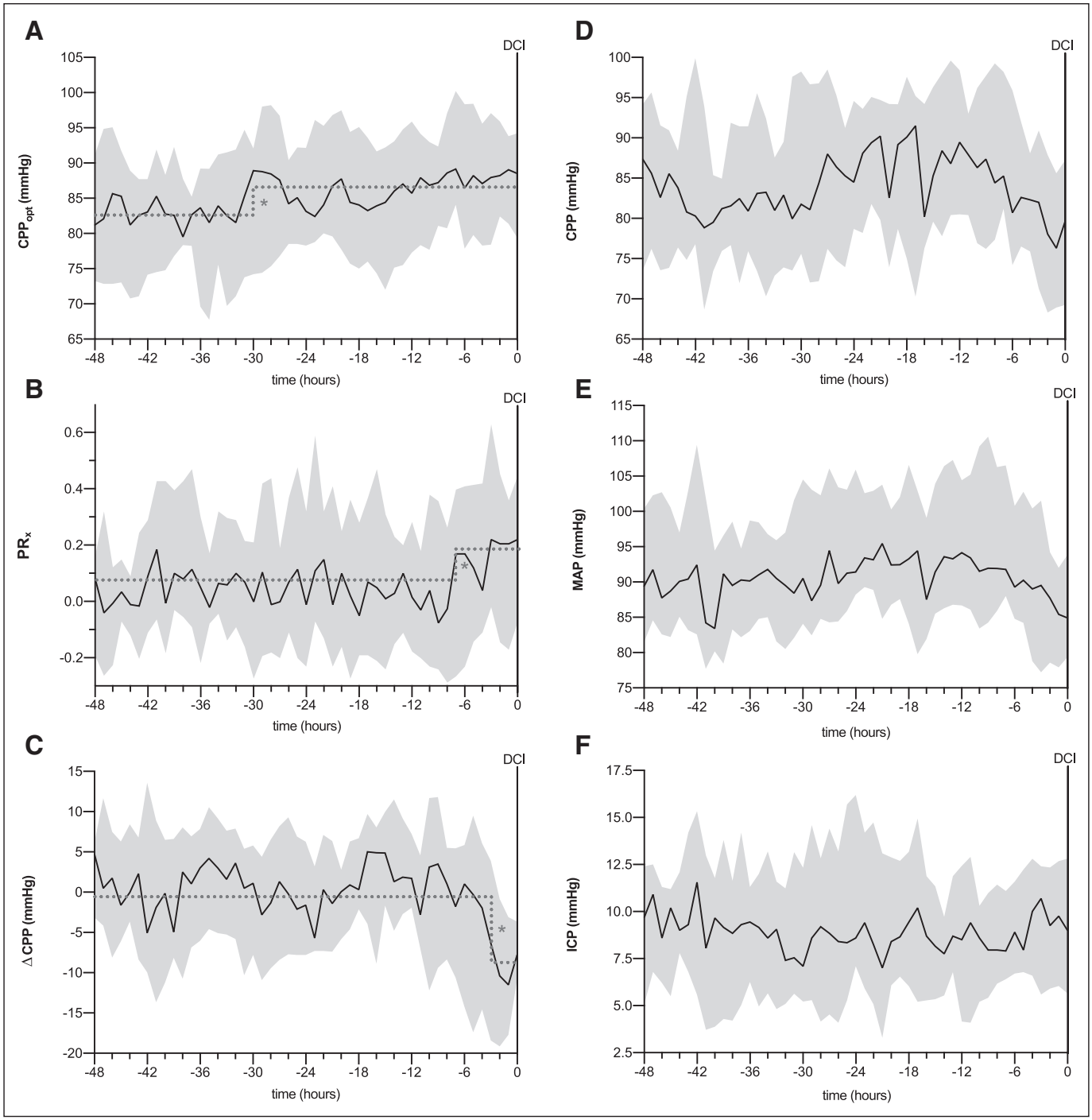

Figure 2. Hemodynamic parameters 48 hr prior to delayed cerebral ischemia (DCI) diagnosis with hourly medians and quartiles (*gray area*). **A**, A significant changepoint in optimal cerebral perfusion pressure (CPP_{opt}) is detected 30 hr before DCI (24). **B** and **C**, Shortly before DCI, the difference of CPP and CPP_{opt} (ΔCPP) becomes negative with a corresponding increase in pressure reactivity index (PR_x). **D–F**, No significant changepoints are identified in cerebral perfusion pressure (CPP), mean arterial pressure (MAP), and intracranial pressure (ICP) despite a negative trend in MAP and CPP prior to DCI.

Response to iHTN

Five patients (25.0%) were refractory to iHTN (iHTN$^-$) and required endovascular rescue treatment on average 16.9 ± 12.6 hours after iHTN. Measurements at time of DCI were comparable (MAP iHTN$^-$ 88.2 ± 8.7 mm Hg, iHTN$^+$ 91.3 ± 7.3 mm Hg, p = 0.51; ICP 9.8 ± 6.1 mm Hg, 7.3 ± 3.1 mm Hg, p = 0.43; CPP 78.3 ± 12.2 mm Hg, 82.5 ± 6.7 mm Hg, p = 0.69; CPP_{opt} 93.1 ± 7.0 mm Hg, 89.0 ± 7.7 mm Hg, p = 0.97; ΔCPP –9.8 ± 11.9 mm Hg, –6.9 ± 6.4 mm Hg, p = 0.51; PR_x 0.19 ± 0.16, 0.20 ± 0.25,

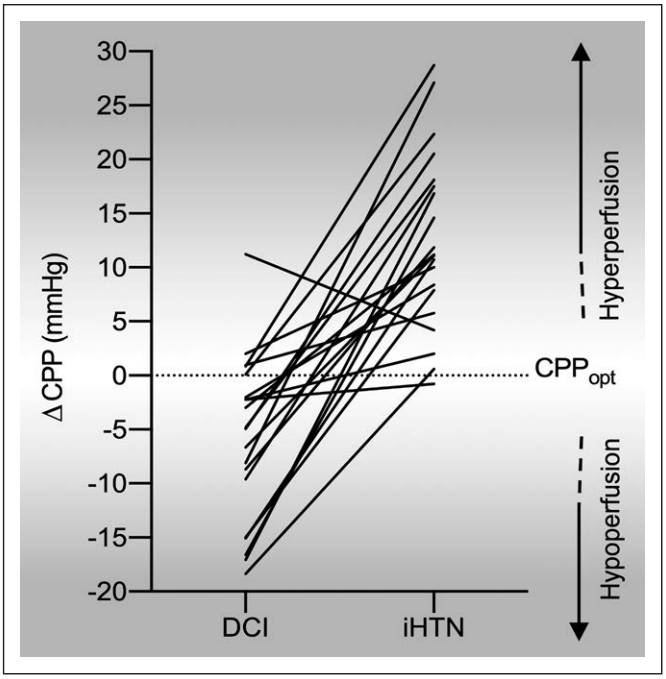

Figure 3. The difference of cerebral perfusion pressure and optimal cerebral perfusion pressure (ΔCPP) at time of delayed cerebral ischemia (DCI) and with induced hypertension (iHTN). Zero represents optimal cerebral perfusion pressure (CPP_{opt}) at the 3-hr baseline prior to DCI diagnosis. Cerebral perfusion pressure (CPP) is predominantly below CPP_{opt} at DCI diagnosis and exceeds CPP_{opt} with iHTN.

$p = 0.63$). Induced CPP did not match CPP_{opt} better in $iHTN^+$ than in $iHTN^-$ patients (ΔCPP_{iHTN} $iHTN^-$ +7.8 ± 4.9 mm Hg, $iHTN^+$ +14.0 ± 8.7 mm Hg; $p = 0.10$).

DISCUSSION

Hypoperfusion at Time of DCI

There is a vast amount of evidence on the deterioration of brain perfusion during DCI (10, 18, 25, 26). However, the necessary blood pressure adjustment to counteract this deficit cannot be quantified by these surrogate variables. Calculating CPP_{opt} may identify an individual level of perfusion necessary for minimizing uncontrolled hypo- or hyperperfusion. Staying within a ± 5 mm Hg range is currently viewed as most beneficial (22). Mean ΔCPP undulated ± 5 mm Hg around zero early before DCI and in patients without DCI (data not shown) but, at time of DCI, the combination of lower CPP and higher CPP_{opt} resulted in a significant decrease of mean ΔCPP to –8 mm Hg. This discrepancy was accompanied by a worsening of autoregulation. The correlation of overall poorer autoregulation in the phase before DCI and its occurrence is established (4, 27), but a deterioration immediately before diagnosis as a (partial) trigger for DCI has not been shown before. We investigated potential reasons for the decrease of ΔCPP prior to DCI and found a higher proportion of infection and a trend for lower overall fluid balance in patients with DCI. Despite rigorous monitoring and treatment, such events cannot be completely avoided. More importantly, most episodes of relative hypotension are currently not recognized as such because blood pressure is within the established limits. Empirical evidence recommends CPP greater than 60–70 mm Hg after aSAH but CPP_{opt} in our cohort was considerably higher, stressing the importance to research individual targets for perfusion.

Hyperperfusion During iHTN

The induced CPP exceeded CPP_{opt} significantly, leading to the assumption that patients may be overtreated to a certain extent. This is important as high doses of vasopressors can be associated with higher systemic complications (28, 29). However, PRx and the CPP_{opt} derived from it represent global parameters, while little is known about regional variance of cerebral autoregulation. It is conceivable that autoregulation could be more disturbed in underserved areas (30); thus, CPP_{opt} could differ considerably (i.e., deviate upwards) in the most critical regions. CPP_{opt} has been primarily validated in traumatic brain injury where such acute, local perfusion mismatch as in DCI is less common. Whether these pathophysiological differences need to be taken into account for interpretation of CPP_{opt} in aSAH remains to be elucidated.

We also aimed to correlate the response to treatment to how well-induced CPP matched CPP_{opt}. This was complicated by the very similar CPP and CPP_{opt} courses, starting with a spontaneous CPP below CPP_{opt} and then exceeding CPP_{opt}. Further mechanisms likely play a role in the responsiveness to iHTN. Severity of DCI may be highly variable between patients but this observation currently escapes any quantification in the absence of a DCI grading scale. More pronounced pathology may be less amenable to any treatment, stressing the importance to control DCI progression before poor functional status is reached.

Outlook

Real-time monitoring of CPP_{opt} can be challenging, requires an invasive ICP-probe at this point, and it is

not clear whether targeting a regularly updated CPP_{opt} is even feasible (22). However, we believe that there is promise in investigating CPPopt after aSAH in more detail. Ultimately, and purely hypothetically, CPP_{opt} could be calculated live on the bedside and blood pressure adjusted accordingly. There is potential that CPP_{opt}-guided blood pressure management could help to optimize blood pressure early on and counteract the development of hypoperfusion before DCI becomes symptomatic. It would be interesting to investigate the occurrence of DCI under these circumstances. A recent trial of early, optimized volume management after aSAH showed such positive effects on DCI, encouraging the principle of live adjustment of hemodynamics (31). Additionally, CPP_{opt}-guided blood pressure management may help prevent futile trials of aggressive iHTN and serve as an indicator to move on to alternative treatment strategies. We propose to conduct larger, prospective investigations on this new concept to assess its usefulness for the management of aSAH.

Limitations

Our study remains limited in terms of statistical power, particularly in subgroup analysis. Furthermore, algorithms for calculating CPP_{opt} were established for traumatic brain injury and have not yet been tested thoroughly on subarachnoid hemorrhage patients, particularly in a setting of iatrogenic blood pressure manipulation, which is why we opted to compare induced CPP to the baseline CPP_{opt} recommendation. Finally, the classical definition of DCI includes deterioration of awake patients only (19). While reaction to hypoperfusion on CTP was deemed reasonable in unconscious patients by neurocritical care guidelines (21), composition of this cohort may still differ from other cohorts investigating DCI.

CONCLUSIONS

Patients with DCI are characterized by significant hypoperfusion in terms of CPP_{opt} at time of deterioration, indicating a need for pressure augmentation at this critical point, for which CPP_{opt} could be a new, objective target parameter. iHTN compensates for the perfusion deficit toward CPP_{opt} but part of this perfusion plus may exceed the requirements. Further investigation of CPP_{opt} in larger, prospective trials is warranted to determine feasibility and effectiveness of real-time CPP_{opt} calculation in aSAH patients, its effect on outcome and its potential in future blood pressure guidance.

1 *Department of Neurosurgery, RWTH Aachen University, Aachen, Germany.*

2 *Program for Hospital and Intensive Care Informatics, Department of Neurology, Columbia University, New York, NY.*

3 *New York Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY.*

4 *Department of Intensive Care, Maastricht University Medical Center, Maastricht University, Maastricht, The Netherlands.*

5 *School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Center, Maastricht, The Netherlands.*

6 *Department of Intensive Care Medicine and Perioperative Care, RWTH Aachen University, Aachen, Germany.*

7 *Department of Diagnostic and Interventional Neuroradiology, RWTH Aachen University, Aachen, Germany.*

Dr. Catharina Conzen was married recently and is now named Catharina Conzen-Dilger.

This study was performed at Department of Neurosurgery, RWTH Aachen University, Aachen, Germany.

Dr. Wiesmann received funding from Stryker Neurovascular, Bracco Imaging, Medtronic, Penumbra, Siemens Healthcare, Abbott, AB Medica, Acandis, Asahi Intecc, Bayer, Bracco Imaging, B. Braun, Cerenovus, Codman Neurovascular, Dahlhausen, Kaneka Pharmaceuticals, Medtronic, Mentice AB, Microvention, Penumbra, Phenox, Philips Healthcare, Route 92, Siemens Healthcare, SilkRoad Medical, St. Jude, and Stryker Neurovascular. Dr. Park's institution received funding from the National Institutes of Health (NIH, R21NS113055), and she received support for article research from the NIH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: gerrit.schubert@me.com

REFERENCES

1. Geraghty JR, Testai FD: Delayed cerebral ischemia after subarachnoid hemorrhage: Beyond vasospasm and towards a multifactorial pathophysiology. *Curr Atheroscler Rep* 2017; 19:50
2. Foreman B: The pathophysiology of delayed cerebral ischemia. *J Clin Neurophysiol* 2016; 33:174–182
3. Jaeger M, Schuhmann MU, Soehle M, et al: Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke* 2007; 38:981–986
4. Gaasch M, Schiefecker AJ, Kofler M, et al: Cerebral autoregulation in the prediction of delayed cerebral ischemia and clinical outcome in poor-grade aneurysmal subarachnoid hemorrhage patients. *Crit Care Med* 2018; 46:774–780

5. Czosnyka M, Smielewski P, Kirkpatrick P, et al: Continuous monitoring of cerebrovascular pressure-reactivity in head injury. *Acta Neurochir Suppl* 1998; 71:74–77
6. Steiner LA, Czosnyka M, Piechnik SK, et al: Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002; 30:733–738
7. Rasulo FA, Girardini A, Lavinio A, et al: Are optimal cerebral perfusion pressure and cerebrovascular autoregulation related to long-term outcome in patients with aneurysmal subarachnoid hemorrhage? *J Neurosurg Anesthesiol* 2012; 24:3–8
8. Silverman A, Kodali S, Strander S, et al: Deviation from personalized blood pressure targets is associated with worse outcome after subarachnoid hemorrhage. *Stroke* 2019; 50:2729–2737
9. Steiner T, Juvela S, Unterberg A, et al; European Stroke Organization: European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; 35:93–112
10. Jafri H, Diringer MN, Allen M, et al: Burden of cerebral hypoperfusion in patients with delayed cerebral ischemia after subarachnoid hemorrhage. *J Neurosurg* 2019; 132:1872–1879
11. Johnson U, Engquist H, Lewén A, et al: Increased risk of critical CBF levels in SAH patients with actual CPP below calculated optimal CPP. *Acta Neurochir (Wien)* 2017; 159:1065–1071
12. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; 43:1711–1737
13. Brown RJ, Kumar A, McCullough LD, et al: A survey of blood pressure parameters after aneurysmal subarachnoid hemorrhage. *Int J Neurosci* 2017; 127:51–58
14. Gathier CS, van den Bergh WM, van der Jagt M, et al; HIMALAIA Study Group: Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: A randomized clinical trial. *Stroke* 2018; 49:76–83
15. Liu X, Maurits NM, Aries MJH, et al: Monitoring of optimal cerebral perfusion pressure in traumatic brain injured patients using a multi-window weighting algorithm. *J Neurotrauma* 2017; 34:3081–3088
16. von Elm E, Altman DG, Egger M, et al: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *BMJ* 2007; 335:806–808
17. Weiss M, Conzen C, Mueller M, et al: Endovascular rescue treatment for delayed cerebral ischemia after subarachnoid hemorrhage is safe and effective. *Front Neurol* 2019; 10:136
18. Albanna W, Weiss M, Müller M, et al: Endovascular rescue therapies for refractory vasospasm after subarachnoid hemorrhage: A prospective evaluation study using multimodal, continuous event neuromonitoring. *Neurosurgery* 2017; 80:942–949
19. Vergouwen MD, Vermeulen M, van Gijn J, et al: Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: Proposal of a multidisciplinary research group. *Stroke* 2010; 41:2391–2395
20. Hutchinson P, O'Phelan K; Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring: International multidisciplinary consensus conference on multimodality monitoring: Cerebral metabolism. *Neurocrit Care* 2014; 21(Suppl 2):S148–S158
21. Diringer MN, Bleck TP, Claude Hemphill J 3rd, et al; Neurocritical Care Society: Critical care management of patients following aneurysmal subarachnoid hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care* 2011; 15:211–240
22. Beqiri E, Smielewski P, Robba C, et al: Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: The COGiTATE phase II study protocol. *BMJ Open* 2019; 9:e030727
23. Czosnyka M, Smielewski P, Kirkpatrick P, et al: Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery* 1997; 41:11–17; discussion 17–19
24. Killick R, Eckley IA. Changepoint: An R package for changepoint analysis. *J Stat Softw* 2014; 58:1–19
25. Cremers CH, van der Schaaf IC, Wensink E, et al: CT perfusion and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *J Cereb Blood Flow Metab* 2014; 34:200–207
26. Yousef KM, Balzer JR, Crago EA, et al: Transcranial regional cerebral oxygen desaturation predicts delayed cerebral ischaemia and poor outcomes after subarachnoid haemorrhage: A correlational study. *Intensive Crit Care Nurs* 2014; 30:346–352
27. Budohoski KP, Czosnyka M, Smielewski P, et al: Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: A prospective observational study. *Stroke* 2012; 43:3230–3237
28. Otsubo H, Takemae T, Inoue T, et al: Normovolaemic induced hypertension therapy for cerebral vasospasm after subarachnoid haemorrhage. *Acta Neurochir (Wien)* 1990; 103:18–26
29. Alkhachroum A, Megjhani M, Terilli K, et al. Hyperemia in subarachnoid hemorrhage patients is associated with an increased risk of seizures. *J Cereb Blood Flow Metab* 2020; 40:1290–1299
30. Hecht N, Schrammel M, Neumann K, et al: Perfusion-dependent cerebral autoregulation impairment in hemispheric stroke. *Ann Neurol* 2021; 89:358–368
31. Anetsberger A, Gempt J, Blobner M, et al: Impact of goal-directed therapy on delayed ischemia after aneurysmal subarachnoid hemorrhage: Randomized controlled trial. *Stroke* 2020; 51:2287–2296