UC Davis

UC Davis Previously Published Works

Title

Deviation From Personalized Blood Pressure Targets Is Associated With Worse Outcome After Subarachnoid Hemorrhage.

Permalink

https://escholarship.org/uc/item/8xt529wc

Journal

Stroke, 50(10)

ISSN

0039-2499

Authors

Silverman, Andrew
Kodali, Sreeja
Strander, Sumita
et al.

Publication Date

2019-10-01

DOI

10.1161/strokeaha.119.026282

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

Stroke. 2019 October ; 50(10): 2729–2737. doi:10.1161/STROKEAHA.119.026282.

Deviation from personalized blood pressure targets is associated with worse outcome after subarachnoid hemorrhage

Andrew Silverman, ScB[1], **Sreeja Kodali, BS**[1], **Sumita Strander, BA**[1], **Emily J. Gilmore, MD**[1], **Alexandra Kimmel, BA**[1], **Anson Wang, BS**[1], **Branden Cord, MD**[2], **Guido Falcone, MD**[1], **Ryan Hebert, MD**[2], **Charles Matouk, MD**[2], **Kevin N. Sheth, MD**[1], **Nils H. Petersen, MD**[1]

[1]Department of Neurology, Yale Medical School, New Haven, CT

[2]Department of Neurosurgery, Yale Medical School, New Haven, CT

Abstract

Background and Purpose: Optimal blood pressure (BP) management during the early stages of aneurysmal subarachnoid hemorrhage (aSAH) remains uncertain. Observational studies have found worse outcomes in patients with increased hemodynamic variability, suggesting BP optimization as a potential neuroprotective strategy. In this study, we calculated personalized BP targets at which cerebral autoregulation was best preserved. We analyzed how deviation from these limits correlates with functional outcome.

Methods: We prospectively enrolled 31 patients with aSAH. Autoregulatory function was continuously measured by interrogating changes in near-infrared spectroscopy (NIRS)-derived tissue oxygenation – a surrogate for cerebral blood flow – as well as intracranial pressure (ICP) in response to changes in mean arterial pressure (MAP) using time-correlation analysis. The resulting autoregulatory indices were used to identify the upper and lower limit of autoregulation. Percent time that MAP exceeded limits of autoregulation was calculated for each patient. Functional outcome was assessed using the modified Rankin Scale (mRS) at discharge and 90 days. Associations with outcome were analyzed using ordinal multivariate logistic regression.

Results: Personalized limits of autoregulation (LA) were computed in all patients (age 57.5±13.4, 23F, mean WFNS 2±1, monitoring time 67.8±50.8 hours). Optimal BP and LA were calculated on average for 89.5±6.7% of the total monitoring period. ICP- and NIRS-derived optimal pressures strongly correlated with one another (P<0.0001). Percent time that MAP deviated from LA significantly associated with worse functional outcome at discharge (NIRS P=0.001, ICP P=0.004) and 90 days (NIRS P=0.002, ICP P=0.003), adjusting separately for age, WFNS, vasospasm, and delayed cerebral ischemia.

Conclusions: Both invasive (ICP) and non-invasive (NIRS) determination of personalized BP targets after aSAH is feasible, and these two approaches revealed significant collinearity.

Correspondence: Nils Petersen, Yale Medical School, 15 York St, LLCI 1000C, New Haven, CT 06510, Nils.Petersen@yale.edu, Andrew Silverman, Yale Medical School, 15 York St, New Haven, CT 06510, Andrew.Silverman@yale.edu.

Disclosures

AS and NHP declare no competing interests.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Furthermore, exceeding individualized limits of autoregulation was associated with poor functional outcomes.

Keywords

Subarachnoid hemorrhage; Cerebral blood flow; Cerebrovascular disease; Cerebral autoregulation

Introduction

Despite advances in critical care, aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease affecting approximately 30,000 adults in the United States per year.[1] Forty percent of aSAH patients die within 30 days, and over one-third of survivors sustain major neurologic deficits. The initial bleed triggers inflammatory cascades, vasospasm, microthrombosis, and cortical spreading depolarizations, all of which likely contribute to delayed cerebral ischemia (DCI).[2] The relationship between DCI and any one of these pathophysiologic mechanisms, however, is non-linear. Instead, these mechanisms likely represent a constellation of pathophysiology, rendering patients vulnerable to secondary neurologic injury. In particular, early impairment of cerebral autoregulation in the setting of vasospasm may compromise the brain's ability to compensate for hemodynamic instability, as may occur during an episode of hypotension.[3,4]

In the uninjured brain, cerebral blood flow autoregulation protects the brain from a wide range of perfusion pressures.[5] Following aSAH, local decline in perfusion pressure from vasospasm and/or global reductions of perfusion pressure from hydrocephalus can overwhelm an individual's autoregulatory capacity. Furthermore, the autoregulatory curve can dynamically shift across and within individual patients, providing a strong rationale for personalizing blood pressure (BP) management after aSAH.[3]

Nevertheless, the role of cerebral autoregulation in aSAH is not fully understood. It has been shown that autoregulatory failure is associated with secondary brain injury, possibly leading to cerebral infarctions and poor outcome.[6,7] One of the most commonly employed autoregulatory indices is the pressure reactivity index (PRx) based on intracranial pressure (ICP); high PRx indices, which reflect dysautoregulation, have been associated with morbidity and mortality in aSAH.[8] Another index of autoregulation can be derived using a non-invasive technique, near-infrared spectroscopy (NIRS).[9] Like PRx, the NIRS-derived autoregulatory index has been linked to DCI and poor outcomes in aSAH.[7,10,11] Prior work by our group has shown that NIRS monitoring can be used to identify BP ranges in individual patients at which autoregulation is optimally functioning.[12] Such an autoregulation-derived, personalized BP range may provide a favorable physiologic environment for the injured brain.[13] This concept is critical in the evolving era of personalized medicine, particularly as it remains unclear which patients are ideal candidates for therapeutic BP manipulation.

In this study, we employed a novel methodology to trend autoregulatory BP thresholds in individuals with aSAH to determine patient-specific blood pressure targets. This approach involved both invasive (ICP) and non-invasive (NIRS) continuous measures of cerebral autoregulation and optimal BP ranges. The aim of this pilot study was first to evaluate the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

feasibility of this approach, second to correlate invasive and non-invasive measures of autoregulatory limits, and third to assess the association of deviation from individualized BP targets on radiographic and clinical outcomes following aSAH.

Methods

The authors declare that all supporting data are available within the article and its online supplementary materials.

Study Design and Subjects

This was a single-center, prospective cohort study. All patients presenting to the Yale-New Haven Hospital Emergency Department with the diagnosis of acute SAH were screened. Patents were eligible for enrollment if they were older than 18, were diagnosed with an aneurysmal SAH secondary to a ruptured aneurysm, required invasive BP monitoring in the Neuroscience ICU, and were able to have optimal BP monitoring initiated within 48 hours of symptom onset (prior to possible development of vasospasm). Patients were excluded in the event of a traumatic SAH or other non-aneurysmal condition. History of prior SAH or a modified Rankin scale >2 before admission were additional exclusion criteria.

Per standard of care, all patients received PO nimodipine. Treatment protocol aimed to maintain ICP less than 22 mmHg and cerebral perfusion pressure (CPP) greater than 50 mmHg. If CPP dropped below 50 mmHg, IV norepinephrine or phenylephrine was administered. To treat clinical vasospasm, hypertension with the same vasopressors was induced. If unsuccessful, verapamil was administered during angiography; in 29.0% (9/31) of cases in our cohort, balloon angioplasty was also performed.

The local institutional review board approved this study prior to patient recruitment. All patients or their legally authorized representatives provided written informed consent.

Near-Infrared Spectroscopy and Intracranial Pressure

Adhesive NIRS probes were placed on the frontotemporal scalp covering cortex typically supplied by the middle cerebral artery. These probes connected to the Casmed Foresight Elite monitor (Casmed, USA), which measured oxy- and deoxyhemoglobin concentrations. The ratio of oxyhemoglobin to total hemoglobin (TOI) functions as a cerebral blood flow surrogate and is unaffected by extracranial circulation, hemoglobin concentration, cranial thickness, and cerebrospinal fluid.[9,14] Cerebral vasoreactivity mediates autoregulation through local vasoconstriction and vasodilation with ensuing fluctuations in cerebral blood flow and volume.[15] Autoregulatory function, therefore, can be measured by interrogating changes in TOI or ICP in response to MAP fluctuations. Arterial BP was monitored invasively through the femoral or radial artery. ICP was recorded using an external ventricular drain (EVD). NIRS, ICP, and BP data were collected continuously for up to 1 week following symptom onset, beginning within 48 hours of symptom onset. All signals were sampled at a frequency of 200 Hz and recorded using ICM+ software (Version 8.4, Cambridge, UK).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Calculation of Autoregulatory Indices

Arterial BP and cerebral blood flow emerge as dynamic physiologic oscillations, and their relationship can be characterized via time-correlation analysis. Indices of autoregulation, including the pressure reactivity index (PRx) and tissue oxygenation index (TOx), are calculated as rolling correlation coefficients between successively averaged MAP values and corresponding ICP or TOI signals, as previously described by Czosnyka et al.[10,15,16] MAP maintains a negative or near-zero correlation with ICP or TOI when autoregulation is functional, indicating pressure-reactive brain blood flow. In contrast, MAP positively correlates with ICP or TOI when autoregulation is impaired, whereby systemic pressures passively propagate to cerebral vasculature.

Calculation of Optimal Blood Pressure (MAP_{OPT})

Regarding determination of MAP_{OPT} in individual patients, 5-minute median MAP time trends were computed alongside PRx and TOx. MAP values were allotted into bins of 5 mmHg; corresponding PRx and TOx indices were averaged within these groups.[13] Parabolic curve fitting was applied to the binned pressures to illustrate the MAP value with the lowest associated PRx or TOx (i.e., the MAP at which autoregulation was most preserved).[17] The nadir of this curve reflects MAP_{OPT}. The MAP at which PRx or TOx crosses a threshold for impaired autoregulation (set at PRx or TOx=+0.30) yields lower and upper limits of autoregulation (LLA, ULA).[18,19] A continuous time trend of MAP_{OPT} and its limits is thus calculated and recorded using a moving 4-hour window that is updated every minute (Figure 1).

Clinical Outcomes

The modified Rankin scale (mRS) was used to assess functional outcome at discharge and 3 months. Unfavorable outcome was defined as mRS ≥3. A blinded member of the research team determined 90-day mRS outcomes via telephone interview. Patients were also assessed for shifts across the entire mRS spectrum.[20]

Clinical Scores and Radiographic Outcomes

All patients were assigned a Hunt & Hess (HH), modified Fisher (mF), and World Federation of Neurologic Surgeons (WFNS) score upon diagnosis of SAH. All patients underwent diagnostic and/or therapeutic cerebral angiogram as part of routine clinical care. When possible, daily transcranial Doppler (TCD) was performed during the week after aSAH treatment. Further imaging with CT, MRI, or additional angiograms was dependent on the treating clinical team and, therefore, patient-specific. Sonographic cerebral vasospasm was defined using acceleration of TCD mean blood flow velocity (mBFV) and the Lindegaard ratio (LR): mild (mBFV>120 cm/s in the middle or anterior cerebral artery, LR 3–6), moderate (mBFV 150–200 cm/s, LR 3–6), or severe (mBFV>200 cm/s, LR>6).[21,22] Radiographic vasospasm was defined using CTA, MRA, or catheter angiography: mild (<30% luminal narrowing relative to normal widths of vessels), moderate (30–50% luminal narrowing), or severe (>50% luminal narrowing).[21] Clinical vasospasm was noted as new focal neurologic signs or deterioration in level of consciousness when other causes of worsening had been excluded. Irrespective of vasospasm, DCI was defined as cerebral

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

infarction on CT or MRI associated with neurologic worsening that could not otherwise be explained.[23,24] All clinical scores and radiographic definitions were confirmed in regular adjudication meetings, including 2 staff neurointensivists (EG, NP) who were blinded to autoregulatory data and all further analyses.

Statistical Analysis

In each patient, we calculated percent time spent outside the limits of autoregulation (%time outside LA). We used generalized linear models (GLM) to test for associations among %time outside LA and vasospasm, DCI, discharge and 3-month outcome. The GLM modeled ordinal logistic regression to assess for shifts across the mRS range. In multivariate analysis, we accounted for independent variables that have been associated with outcome after aSAH, including age, WFNS, clinical vasospasm, and DCI. Due to the small sample size, the multivariate model could only adjust for two covariates at a time. Therefore, separate adjustments for age, WFNS, clinical vasospasm, and DCI were carried out. Predictive performance of %time outside LA for poor outcome was analyzed via area under the receiver operating characteristic (ROC) curve.

Results

Demographics

Thirty-one patients were enrolled (Table 1). Mean NIRS monitoring time was 67.80 (±50.83) hours. Optimal BP could be calculated for a mean of 89.53 (±6.69)% of the total NIRS monitoring period. Patients spent on average 69.13 (±18.93)% of their monitored time within LA (Supplemental Table I). Among patients with good and poor outcome at discharge and 90 days, lower and upper limits of autoregulation were not different. BP variability, computed as the standard deviation of MAP during the monitoring period, was also not significantly different between these groups, though a trend toward greater variability was observed in patients with worse discharge outcomes (8.1 *vs.* 16.6 mmHg, P=0.106). Patients with favorable outcome at discharge were younger and endured angiographic vasospasm and DCI less frequently. They also had lower TOx and PRx indices (i.e., more intact autoregulation), wider NIRS-derived optimal BP ranges, and spent less time outside their dynamic optimal BP ranges (Supplemental Tables II&III).

Autoregulatory Indices and Outcome

In univariate analysis, TOx associated significantly with functional outcome at discharge (P=0.001, OR 3.0, 95% CI 1.5–5.8) and 90 days (P=0.006, OR 2.5, 95% CI 1.3–4.8; Supplemental Tables IV&V). These associations held when adjusting separately for age, WFNS, vasospasm, and DCI (Supplemental Tables VI&VII). PRx significantly associated with discharge mRS (P=0.010, OR 6.3, 95% CI 1.6–25.6) and 90-day mRS (P=0.016, OR 5.6, 95% CI 1.4–22.6). These associations held when adjusting separately for age, WFNS, and vasospasm.

NIRS- and ICP-derived MAP_{OPT} (Spearman 0.93, P<0.0001), LLA (Spearman 0.88, P<0.0001), and ULA (Spearman 0.90, P<0.0001) demonstrated strong correlations with one another (Figure 2). Additional Bland-Altman analyses of NIRS- vs. ICP-derived

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

autoregulatory parameters further demonstrated agreement between these modalities (Supplemental Figure I).

Limits of Autoregulation and Clinical Outcome

Using ICP-derived optimal blood pressures, %time outside LA was a significant predictor of unfavorable outcome at discharge (P=0.003, OR 2.6, 95% CI 1.4–4.9) and 90 days (P=0.004, OR 2.8, 95% CI 1.4–5.5) (Figure 3A&B). Every 10% increase in time spent outside LA was associated with a 2.8-fold increase in the odds of shifting towards a worse outcome on the 90-day mRS. These associations remained significant after separate adjustments for age, WFNS, vasospasm, and DCI (Supplemental Tables VI&VII).

Using NIRS-derived optimal blood pressures, %time outside LA significantly associated with poor discharge (P=0.0004, OR 2.2, 95% CI 1.4–3.4) and 90-day outcome (P=0.002, OR 1.9, 95% CI 1.3–2.9) (Figure 3C&D). These associations remained significant after separate adjustments for the same covariates (Supplemental Tables VI&VII). Deviation from NIRS-derived autoregulatory limits predicted poor discharge and 90-day outcome with high sensitivity and specificity (area under ROC 0.82, 95% CI 0.67–0.98, P=0.003 and 0.88, 95% CI 0.76–1.00, P=0.001, respectively; Supplemental Figure II).

Three patients underwent treatment for clinical vasospasm during the neuromonitoring period; the remaining cohort did not undergo hemodynamic interventions for vasospasm during recordings. Given the possible effect of BP interventions on autoregulatory function, a sensitivity analysis was performed excluding these patients. After separate adjustments for age, WFNS, vasospasm, and DCI, NIRS- and ICP-derived %time outside LA remained significantly associated with discharge and 90-day outcomes (Supplemental Tables XIII&IX).

Limits of Autoregulation and Radiographic Outcomes

Six patients suffered from DCI (19.4%). Percent time with MAP outside LA did not significantly differ between patients with and without any short-term radiographic outcomes (Table 2). Nonetheless, when comparing patients with and without DCI, a trend toward more time spent outside LA can be seen for NIRS and ICP modalities (Supplemental Figure III).

Discussion

In this pilot feasibility study of 31 patients with aSAH, we demonstrated that continuous estimation of optimal blood pressure and limits of cerebral autoregulation is feasible and that deviation from personalized thresholds of autoregulation associates with worse functional outcome. We also showed collinearity between invasively (ICP) and non-invasively (NIRS) derived optimal blood pressures and limits of autoregulation, providing support for non-invasive measures of autoregulation in patients who may not be candidates for invasive procedures.

Observational studies performed in patients with traumatic brain injury suggest that autoregulatory physiology can be harnessed to optimize cerebral perfusion.[25,26] Although not yet proven in prospective studies, retrospective data suggest that this treatment avenue

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

may ameliorate outcome after brain injury. Similar findings in patients with aSAH have posited that intact autoregulation improves clinical outcomes.[3,4,6] Furthermore, autoregulatory function was invoked as a secondary endpoint in aSAH clinical trials of pravastatin and erythropoietin, both of which reduced the duration of impaired autoregulation in tandem with improved discharge outcomes, a decrease of in-hospital mortality, and a marked decrease in DCI.[27–29] Of note, functional improvements were not sustained in 6-month follow-up. These two trials, therefore, illustrate that targeting autoregulation is achievable as a therapeutic paradigm, but the ultimate benefit of such a strategy remains unclear.

While these studies considered autoregulation in their design, no prospective study has examined personalized BP thresholds based on autoregulatory physiology following aneurysmal rupture. Optimal BP ranges are unique to individual patient physiology and likely influenced by numerous factors.[3–5] For example, disturbances in autoregulation may be exacerbated when cerebral vessels are unable to adjust for vasoconstriction caused by proximal spasm. This dual insult of vasospasm and dysfunctional autoregulation may shorten the autoregulatory plateau and render patients vulnerable to distal ischemia. In comparison, microvascular spasm may shift the autoregulatory curve towards higher pressures.[30] For these reasons, evaluating individual patients' hemodynamics and maintaining BP within autoregulatory limits may provide a favorable physiologic environment for the injured brain.

Indeed, in our study, for every 10% increase in time spent outside ICP-derived limits of autoregulation, there was a 2.6-fold and 2.8-fold increased likelihood of shifting towards worse outcomes on the discharge and 3-month mRS, respectively. Importantly, our neuromonitoring was initiated within the first 48 hours of aneurysm rupture, well before the vasospasm risk window. In addition, a sensitivity analysis excluding patients who underwent treatment for clinical vasospasm revealed persistent significance between %time outside LA and functional outcome. These results suggest that deviation from optimal BP targets in the early days following aSAH may help to identify patients who are more susceptible to further damage from hemodynamic instability (i.e., relative hypo- or hyperperfusion) throughout their hospital course. Additionally, patients with worse discharge and 90-day outcomes exhibited narrower NIRS-derived optimal BP target ranges consistent with a shortening of their autoregulatory plateau.

Although associations between PRx and functional outcome are well established in patients with traumatic brain injury, less robust evidence exists for patients with SAH.[8] Mixed results have been reported in recent literature, but in general studies have demonstrated a strong relationship among high PRx indices, DCI, and poor outcome.[31–33] Most of these studies used measurements of ICP when the EVD is closed, but Aries et al. effectively showed that an open EVD system can be harnessed to calculate autoregulatory indices due to preserved slow fluctuations in the ICP signal.[34] More recently, Klein et al. revealed good agreement of PRx indices obtained via parenchymal and EVD measurements of ICP.[35] In our study, then, we included continuous ICP data to derive dynamically updating optimal BP parameters regardless of whether the EVD was open. This inclusive approach resulted in longer

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

monitoring periods and an increased capacity to determine ideal BP in real-time. Ultimately, higher PRx indices correlated with worse outcomes in our cohort.

Similar findings have been reported using non-invasive technologies like TCD and NIRS. Budohoski et al. found that perturbed autoregulation in the first 5 days after aSAH was associated with DCI and poor outcome.[7] These authors not only highlighted the feasibility of detecting dysautoregulation using NIRS, but they also observed collinearity between TCD- and NIRS-based indices of autoregulation. Using these results as a launchpad, our study underscores the feasibility of using both invasive and non-invasive measures of autoregulation-based optimal BP. Further, we showed that target BP ranges significantly correlated between NIRS and ICP modalities, providing an argument for non-invasive measures of optimal cerebral perfusion pressure in future studies.

This study has several limitations, including a small sample size. This small sample size precluded sufficient multivariate analysis. As a result, we recursively performed multiple sensitivity analyses with two covariates at a time to support our hypothesis that time outside limits of autoregulation is not simply an epiphenomenon, but is independently associated with clinical outcome, thereby representing a possible therapeutic target. Given the study's observational design, conclusions about the effect of autoregulation-guided therapy on outcome are beyond its scope. Indeed, the study cannot determine causality, only correlation. While inferences about autoregulatory mechanisms underlying DCI are clouded because only 6 patients suffered from this complication, a recent meta-analysis found that autoregulatory impairment likely constitutes an accurate predictor of DCI and poor outcome.[36] These authors performed a summary receiver operating characteristic of autoregulation disturbances for DCI prediction, reporting an area under the curve of 0.87, underlining autoregulation's clinical import in prognostication. In our study, while %time outside LA did not significantly differ in patients with and without DCI, there was an appreciable trend towards spending more time outside LA in patients with DCI. This interesting observation would align with Harper's dual insult theory, whereby dysautoregulation distal to proximal vasospasm results in infarction.[3,4,37,38] In a larger cohort, prospective randomized trials using continuous monitoring strategies to calculate optimal BP targets may help to bridge this knowledge gap. Lastly, our neuromonitoring was performed early after admission before patients were at risk for vasospasm; beginning at this time point was by design, but completing some recordings prior to vasospasm was dictated by practical issues, including discontinuation of ICP monitoring by the clinical team, recording equipment availability, and discharge from the ICU. More longitudinal monitoring is warranted to capture granular temporal dynamics of optimal BP targets during and after risk periods of vasospasm and DCI.

Conclusion

Our method of continuous estimation of autoregulatory limits patients provides a BP range tailored to patients' individual hemodynamics. This study thus constitutes an innovative approach to determine patient-specific dynamic BP targets and provides an impetus for further research into hemodynamic-oriented neuroprotective therapies.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Funding

This work was supported by the American Heart Association Founders Affiliate Grant#18-05-MSF, American Heart Association Grant#17MCRP33460188/NilsPetersen/2017, and Clinical and Translation Science Award (CTSA) Grant#KL2TR001862 from the National Center for Advancing Translation Science (NCATS), a component of the National Institute of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the American Heart Association or NIH.

Dr. Falcone is conducting research funded by the NIH (K76AG059992 and R03NS112859), the American Heart Association (18IDDG34280056), the Yale Pepper Scholar Award (P30AG021342) and the Neurocritical Care Society Research Fellowship. Dr. Sheth is conducting research funded by the NIH (U24NS107215, U24NS107136, U01NS106513, RO1NR018335) and the American Heart Association (17CSA33550004). He has received funding for lead PI role for INTREPID (Bard), S1P ICH (Novartis), and CHARM (Biogen) stroke studies.

References

1. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al.; AHA Stroke Council, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2012;43:1711–1737. [PubMed: 22556195]
2. Geraghty JR, Testai FD. Delayed Cerebral Ischemia after Subarachnoid Hemorrhage: Beyond Vasospasm and Towards a Multifactorial Pathophysiology. Curr Atheroscler Rep 2017;19:50. [PubMed: 29063300]
3. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, Pickard JD. Clinical relevance of cerebral autoregulation following subarachnoid hemorrhage. Nat Rev Neurol 2013;9:152–63. [PubMed: 23419369]
4. Wang A, Ortega-Gutierrez S, Petersen NH. Autoregulation in the Neuro ICU. Curr Treat Options Neurol 2018;20:20. [PubMed: 29770889]
5. Donnelly J, Budohoski KP, Smielewski P, Czosnyka M. Regulation of cerebral circulation: bedside assessment and clinical implications. Critical Care 2016;20:129. [PubMed: 27145751]
6. Jaeger M, Soehle M, Schuhmann MU, Meixensberger J. Clinical Significance of Impaired Cerebrovascular Autoregulation After Severe Aneurysmal Subarachnoid Hemorrhage. Stroke 2012;43:2097–101. [PubMed: 22618384]
7. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Butlers D, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. Stroke 2012;43:3230–7. [PubMed: 23150652]
8. Gaasch M, Schiefecker AJ, Kofler M, Beer R, Rass V, Psausler B, et al. Cerebral Autoregulation in the Prediction of Delayed Cerebral Ischemia and Clinical Outcome in Poor-Grade Aneurysmal Subarchnoid Hemorrhage Patients. Neurol Crit Care 2018;46:774–780.
9. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke 2001;32:2492–2500. [PubMed: 11692006]
10. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke 2010;41:1963–8. [PubMed: 20651272]
11. Budohoski KP, Czosnyka M, Smielewski P, Varsos GV, Kasprowicz M, Brady KM, et al. Cerebral autoregulation after subarachnoid hemorrhage: comparison of three methods. J Cereb Blood Flow Metab 2013;33:449–56. [PubMed: 23232948]
12. Petersen NH, Silverman A, Wang A, Strander S, Kodali S, Sansing LH, et al. Exceeding Personalized Blood Pressure Targets after Endovascular Stroke Therapy is Associated with Hemorrhagic Transformation and Worse Functional Outcome. JAMA Neurol 2019;in press:E1–3.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

13. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, 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. [PubMed: 11940737]
14. Yoshitani K, Kawaguchi M, Miura N, Okuno T, Kanoda T, Ohnishi Y, et al. Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. Anesthesiology 2007;106:458–462. [PubMed: 17325503]
15. Lee JK, Kibler KK, Benni PB, Easley RB, Czosnyka M, Smielewski P, et al. Cerebrovascular reactivity measured by near-infrared spectroscopy. Stroke 2009;40:1820–1826. [PubMed: 19286593]
16. Czosnyka M, Piechnik S, Richards HK, Kirkpatrick P, Smielewski P, Pickard JD. Contribution of mathematical modelling to the interpretation of bedside tests of cerebrovascular autoregulation. Neurol, Neurosurg & Psych 1997;63:721–731.
17. Aries MJH, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med 2012;40:2456–2463. [PubMed: 22622398]
18. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. Neurocrit Care 2009;10:122–8. [PubMed: 18807218]
19. Donnelly J, Czosnyka M, Adams H, Robba C, Steiner LA, Cardim D, et al. Pressure Reactivity-Based Optimal Cerebral Perfusion Pressure in a Traumatic Brain Injury Cohort. Acta Neurochir Suppl 2018;126:209–212. [PubMed: 29492563]
20. Saver JL. Novel End Point Analytic Techniques and Interpreting Shifts Across the Entire Range of Outcome Scales in Acute Stroke Trials. Stroke 2007;38:3055–3062. [PubMed: 17916765]
21. Etminan N, Beseoglu K, Heiroth HJ, Turowski B, Steiger HJ, Hanggi D. Early perfusion computerized tomography imaging as a radiographic surrogate for delayed cerebral ischemia and functional outcome after subarachnoid hemorrhage. Stroke 2013;44:1260–1266. [PubMed: 23539527]
22. Santos GA, Petersen N, Zamani AA, Du R, LaRose S, Monk A, et al. Pathophysiologic differences in cerebral autoregulation after subarachnoid hemorrhage. Neurology 2016;86:1950–1956. [PubMed: 27164675]
23. Hidra A, van Gijn N, Nagelkerke NJ, Vermeulen M, van Crevel H. Prediction of delayed cerebral iscehmia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. Stroke 1988;19:1250–1256. [PubMed: 3176085]
24. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJE, Wijdicks EF, Muizelaar P, 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. [PubMed: 20798370]
25. Rivera-Lara L, Zorrilla-Vaca A, Geocadin R, Ziai W, Healy R, Thompson R, et al. Predictors of outcome with cerebral autoregulation monitoring: a systematic review and meta-analysis. Crit Care Med 2017;45:695–704. [PubMed: 28291094]
26. Kramer AH, Couillard PL, Zygun DA, Aries MJ, Gallagher CN. Continuous Assessment of “Optimal” Cerebral Perfusion Pressuer in Traumatic Brain Injury: A Cohort Study of Feasibility, Reliability, and Relation to Outcome. Neurocrit Care 2019;30:51–61. [PubMed: 29987688]
27. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. Stroke 2005;36:1627–1632. [PubMed: 16049199]
28. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with statins on cerebral autoregulation in patients after aneurysmal subarachnoid hemorrhage. Neurosurg Focus 2006;21:E10.
29. Tseng MY, Hutchinson PJ, Czosnyka M, Richard H, Pickard JD, Kirkpatrick PJ. Effects of acute pravastatin treatment on intensity of rescue therapy, length of inpatient stay, and 6-month outcome

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

in patients after aneurysmal subarachnoid hemorrhage. Stroke 2007;38:1545–1550. [PubMed: 17413047]

30. Nornes H, Knutzen HB, Wikeby P. Cerebral arterial blood flow and aneurysm surgery. Part 2: induced hypotension and autoregulatory capacity. J. Neurosurg 1977;47:819–827. [PubMed: 925739]
31. Bijlenga P, Czosnyka M, Budohoski KP, Soehle M, Pickard JD, Kirkpatrick PJ, Smielewski P. "Optimal cerebral perfusion pressure" in poor grade patients after subarachnoid hemorrhage. Neurocrit Care 2010;13:17–23. [PubMed: 20405341]
32. Eide PK, Sorteberg A, Bentsen G, Marthinsen PB, Stubhaug A, Sorteberg W. Pressure-derived versus pressure wave amplitude-derived indices of cerebrovascular pressure reactivity in relation to early clinical state and 12-month outcome following aneurysmal subarachnoid hemorrhage. J Neurosurg 2012;116:961–971. [PubMed: 22324419]
33. Barth M, Woitzik J, Weiss C, Muench E, Diepers M, Schmiedek P, et al. Correlation of clinical outcome with pressure-, oxygen-, and flow-related indices of cerebrovascular reactivity in patients following aneurysmal SAH. Neurocrit Care 2010;12:234–243. [PubMed: 19816810]
34. Aries MJH, de Jong SF, van Dijk JMC, Regtien J, Depreitere B, Czosnyka M, et al. Observation of Autoregulation Indices During Ventricular CSF Drainage After Aneurysmal Subarachnoid Hemorrhage: A Pilot Study. Neurocrit Care 2015;23:347–354. [PubMed: 25792344]
35. Klein SP, Bruyninckx D, Callebaut I, Depreitere B. Comparison of intracranial pressure and pressure reactivity index obtained through pressure measurements in the ventricle and in the parenchyma during and outside cerebrospinal fluid drainage episodes in a manipulation-free patient setting. Acta Neurochir Suppl 2018;126:287–290. [PubMed: 29492576]
36. Zhiyuan Y, Zheng J, Ma L, Li H, You C, Jiang Y. Predictive Value of Cerebral Autoregulation Impairment for Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis. World Neurosurg 2019;in press:1–7.
37. Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. J Neurol Neurosurg Psych 1965;28:449–52.
38. Harper AM, Deshmukh VD, Sengupta D, Rowan JO, Jennett WB. The effect of experimental spasm on the CO2 response of cerebral bloodflow in primates. Neuroradiology 1972;3:134–6. [PubMed: 4208041]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

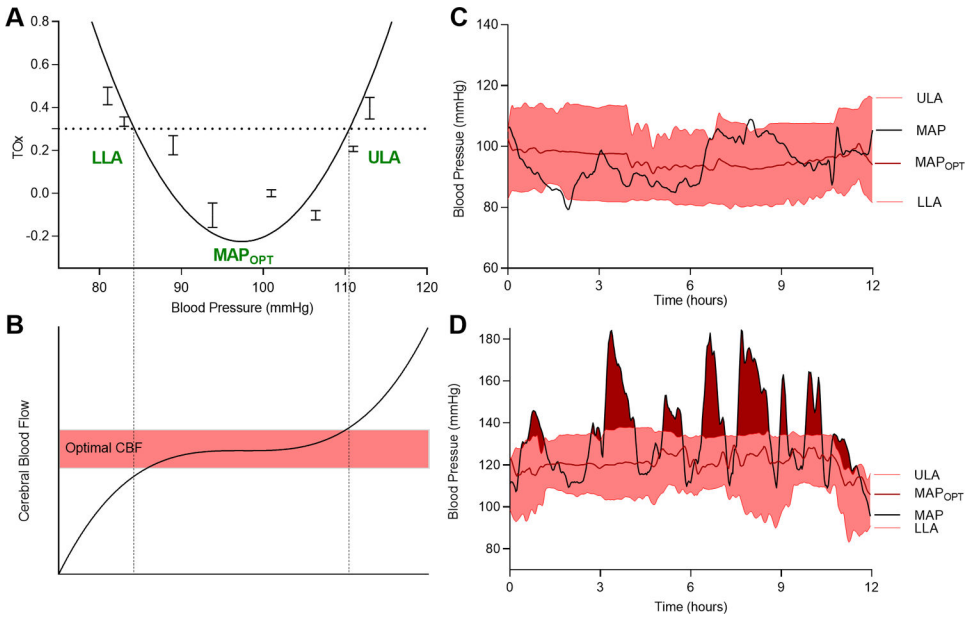

Figure 1. Generation of MAP$_{OPT}$ and personalized limits of autoregulation.

Panel A shows the characteristic parabolic curve that is generated when plotting an autoregulatory index against a range of binned blood pressures during a 4-hour recording. The vertex of this U-curve is located at the point with the lowest autoregulatory index and thus represents the optimum blood pressure (MAP$_{OPT}$). By setting a threshold for impaired autoregulation at TOx=+0.30, intersecting MAP values provide estimates of lower and upper limits of autoregulation (LLA, ULA). These intersections correspond with the inflection points of Lassen's autoregulatory curve, as shown by the dotted vertical lines between Panels A and B. In Panel C, a continuous time trend of these limits can be displayed in real-time, while superimposing the patient's actual BP in black, to provide clinicians with a dynamically updating BP target. Panel D shows another patient's 12-hour recording, during which the patient's blood pressure frequently oscillated outside personalized limits of autoregulation (regions highlighted in dark red above ULA).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

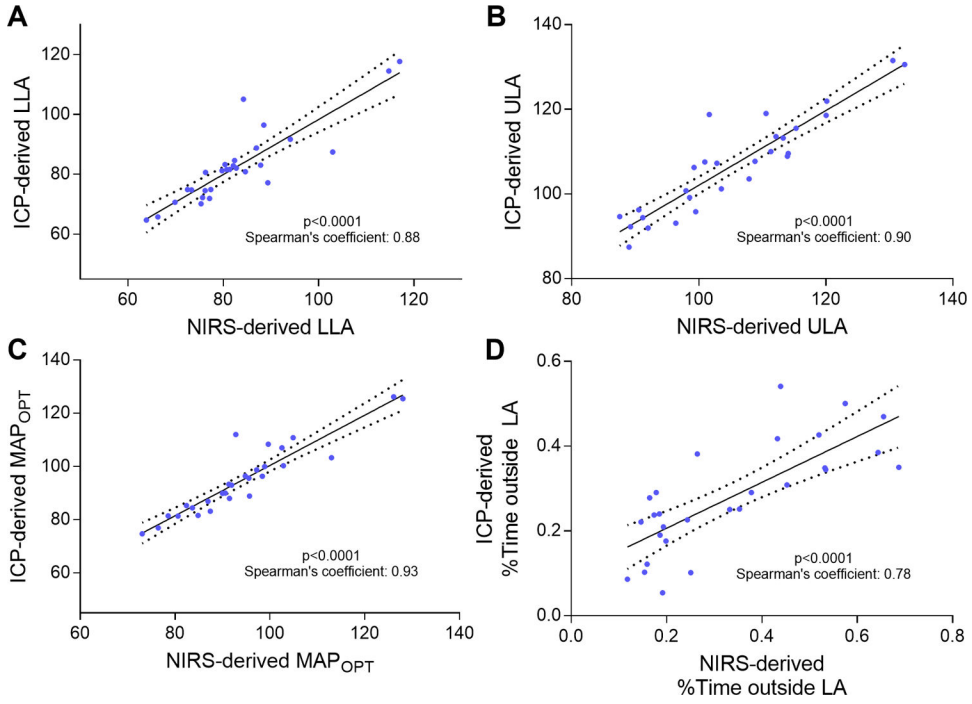

Figure 2. Correlation between ICP- and NIRS-derived limits of autoregulation.

ICP- and NIRS-derived autoregulatory parameters significantly correlated in bivariate non-parametric analysis (Panels A–C). Both ICP- and NIRS-derived %time outside LA also correlated with one another (Panel D). Best-fit lines and corresponding 95% confidence intervals are displayed to illustrate linear relationships. LA: limits of autoregulation.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

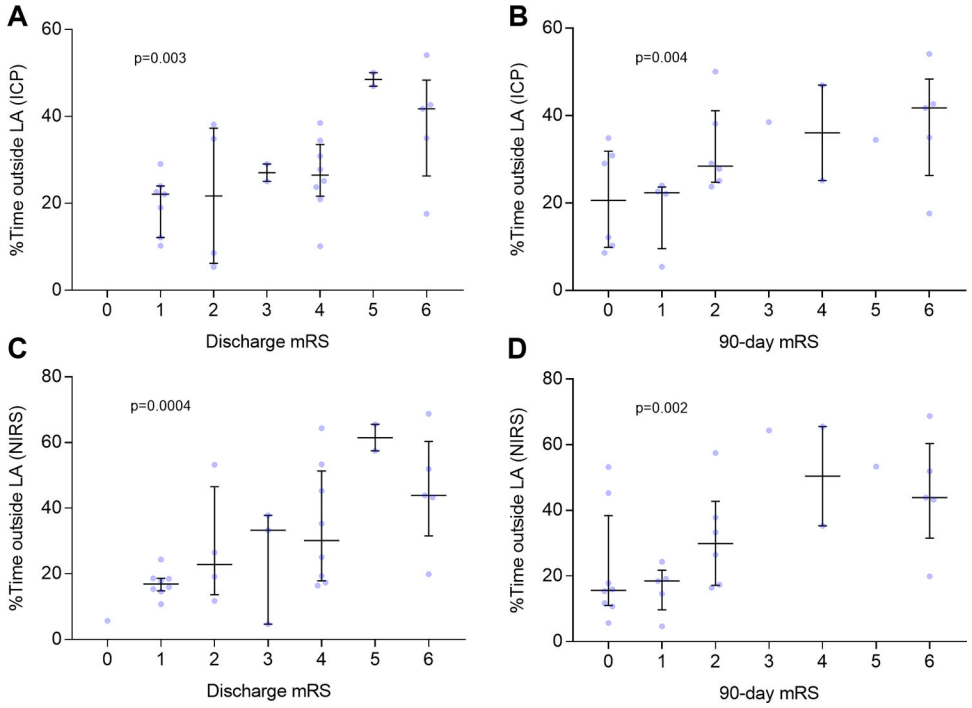

Figure 3. Percent time MAP spent outside limits of autoregulation associates with discharge and 90-day functional outcome following aSAH.

A&B: Deviation from ICP-derived autoregulatory limits associated with discharge and 90-day outcome. **C&D:** Deviation from NIRS-derived autoregulatory limits associated with discharge and 90-day outcome. P-values shown demonstrate statistical significance in univariate ordinal regression. Error bars represent 95% confidence intervals. OR: odds ratio; CI: confidence interval.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Patient Characteristics.

Total patients	31
90-day outcomes, n (%)	28 (90.3)
Gender, F (%)	23 (74.2)
Age, mean ± SD	57.5 ± 13.4
Race	
White	18 (58.1)
Black or African American	6 (19.4)
Hispanic	5 (16.1)
Asian	2 (6.5)
Admission WFNS, mean ± SD	2.2 ± 1.2
Admission HH, mean ± SD	2.7 ± 0.9
Admission mF, mean ± SD	3.2 ± 1.1
Admission MAP, mean ± SD	97.6 ± 19.6
Aneurysm Location, n (%)	
Acomm	12 (38.7)
Pcomm	5 (16.1)
MCA	5 (16.1)
ICA	4 (12.9)
Pericallosal	1 (3.2)
Basilar tip	2 (6.5)
PICA	1 (3.2)
No definitive lesion on angiogram with aneurysmal bleed pattern on head CT	1 (3.2)
Medical History *, n (%)	
Hypertension	13 (41.9)
Coronary Artery Disease	1 (3.2)
Myocardial Infarction	3 (9.7)
Congestive Heart Failure	1 (3.2)
Atrial Fibrillation	1 (3.2)
Hyperlipidemia	11 (35.5)
Diabetes Mellitus (I&II)	4 (12.9)
Cancer	4 (12.9)
Thyroid Disease	4 (12.9)
Migraine	3 (9.7)
Fibromuscular Dysplasia	1 (3.2)
Current Smoker	7 (22.6)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Past Smoker	13 (41.9)
Alcohol Intake (1 drink~12 grams)	
1 (no alcohol consumption)	21 (67.7)
2 (consumption≤150 grams/week)	7 (22.6)
3 (consumption≥150 grams/week)	3 (9.7)
Ictal loss of consciousness, n (%)	13 (41.9)
Endovascular coiling, n (%)	24 (77.4)
Surgical clipping, n (%)	3 (9.7)
EVD placed, n (%)	28 (90.3)
Intubated, n (%)	28 (90.3)
Treated for pneumonia, n (%)	13 (41.9)
Treated for *C. difficile*, n (%)	1 (3.2)
Rebleed, n (%)	2 (6.5)
VP shunt placed, n (%)	1 (3.2)
Length of stay, mean days ± SD	19.3 ± 11.3
Early hydrocephalus, n (%)	17 (54.8)
Vasospasm on TCD, CTA, or MRA, n (%)	15 (48.4)
Angiographic vasospasm, n (%)	9 (29.0)
Clinical vasospasm, n (%)	8 (25.8)
DCI, n (%)	6 (19.4)
In-hospital mortality, n (%)	5 (16.1)
90-day mortality, n (%)	5 (21.5)

Baseline demographics are shown. SD: standard deviation; Acomm: anterior communicating artery; Pcomm: posterior communicating artery; MCA: middle cerebral artery; ICA: internal carotid artery; PICA: posterior inferior cerebellar artery; CT: computed tomography; VP: ventriculoperitoneal; CTA: computed tomography angiography; MRA: magnetic resonance angiography.

*Percentages may add to more than 100% due to comorbidity.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Deviation from autoregulatory limits in patients with and without short-term radiographic and clinical outcome measures.

ICP-derived %time outside LA	**Median**	**IQR**	***P VALUE***
Ictal LoC			0.537
Yes	30.0%	13.0–41.6%	
No	24.6%	19.8–35.0%	
Early Hydrocephalus			1.000
Yes	30.9%	22.1–38.2%	
No	24.0%	15.6–35.9%	
Radiographic Vasospasm			0.701
Yes	31.8%	22.3–40.8%	
No	24.6%	13.5–36.3%	
Angiographic Vasospasm			0.089
Yes	41.8%	29.1–50.1%	
No	24.0%	18.3–32.9%	
Clinical Vasospasm			0.126
Yes	42.2%	27.1–51.1%	
No	24.6%	16.3–34.6%	
DCI			0.126
Yes	45.9%	26.2–53.1%	
No	25.1%	18.0–34.8%	
NIRS-derived %time outside LA	Median	IQR	*P VALUE*
Ictal LoC			0.737
Yes	25.1%	15.9–52.7%	
No	22.1%	17.0–39.2%	
Early Hydrocephalus			0.118
Yes	35.3%	19.2–53.4%	
No	18.6%	15.5–36.7%	
Radiographic Vasospasm			0.740
Yes	24.4%	15.9–53.3%	
No	22.5%	17.0–39.2%	
Angiographic Vasospasm			0.334
Yes	43.6%	19.7–53.0%	
No	19.4%	16.0–37.8%	
Clinical Vasospasm			0.611

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

ICP-derived %time outside LA	Median	IQR	*P VALUE*
Yes	43.3%	17.9–52.0%	
No	22.1%	16.1–43.4%	
DCI			0.105
Yes	43.6%	25.3–54.1%	
No	19.9%	16.0–45.3%	

Using non-parametric comparisons, %time outside LA did not significantly differ in patients with and without ictal loss of consciousness (LoC), early hydrocephalus, radiographic vasospasm, angiographic vasospasm, clinical vasospasm, or delayed cerebral ischemia. IQR: interquartile range.