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Determining the Upper and Lower Limits of Cerebral Autoregulation with Cerebral Oximetry Autoregulation Curves: A Case Series

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Abstract

Objective—Critical care guidelines recommend a single target value for mean arterial blood pressure (MAP) in critically ill patients. However, growing evidence regarding cerebral autoregulation (CA) challenges this concept and supports individualizing MAP targets to prevent brain and kidney hypo- or hyperperfusion. Regional cerebral oxygen saturation (rScO₂) derived from near-infrared spectroscopy (NIRS) is an acceptable surrogate for cerebral blood flow and has been validated to measure CA. These data suggest a novel mechanism to construct autoregulation curves based on NIRS-measured cerebral oximetry.

Design—Case-series study.

Setting—Neurocritical care unit in a tertiary medical center.

Patients—Patients with acute neurologic injury and Glasgow coma scale score ≥ 8.

Measurements and Main Results—Autoregulation curves were plotted using the fractional-polynomial model in Stata after multimodal continuous monitoring of rScO₂ and MAP.

Individualized autoregulation curves of seven patients exhibited varying upper and lower limits of autoregulation and provided useful clinical information on the autoregulation trend (curves

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moving to the right or left during the acute coma period). The median lower and upper limits of autoregulation were 86.5 mmHg (IQR, 74-93.5) and 93.5 mmHg (IQR, 83-99), respectively.

Conclusions—This case-series study showed feasibility of delineating real trends of the CA plateau and direct visualization of the CA curve after at least 24 hours of recording without manipulation of MAP by external stimuli. The integration of multimodal monitoring at the bedside with cerebral oximetry provides a novel, noninvasive method to delineate daily individual CA curves.

Keywords

cerebral oximetry; cerebral perfusion; near-infrared spectroscopy; cerebral autoregulation; autoregulation curve

INTRODUCTION

Growing evidence supports the utility of using multimodal monitoring with near-infrared spectroscopy (NIRS) to measure cerebral autoregulation (CA) and thereby calculate optimal cerebral perfusion pressure (CPP).[1] NIRS is a noninvasive and validated technology to measure CA.[2] NIRS offers two important advantages. First, it provides feasibility to monitor continuous regional cerebral oxygen saturation (rScO₂) at the bedside. Second, it has been proven to be a good surrogate of cerebral blood flow.[3] Three studies have previously shown that patients undergoing cardiac surgery using cardiopulmonary bypass with a mean arterial blood pressure (MAP) below the lower limit of CA, as determined by NIRS, had worse outcomes (renal failure, delirium, postoperative stroke, and mortality) than their counterparts maintained above the lower limit.[4–6]

Since Lassen [7] described the autoregulation curve in 1959, there have been several approximations to plot individualized curves in humans and experimental models, but to date, none have been very successful when using non-invasive techniques.[8–10] Here, we constructed autoregulation curves based on multimodal monitoring with NIRS-derived cerebral oximetry and presented a case where dynamic changes on the CA curve and plateau were captured during the ICU stay. We hypothesized to be able to plot similar CA curves compared to the Lassen's ones using this novel methodology.

METHODS

Type of Study and Patients

This study was conducted in the neurocritical care unit (NCCU) at the Johns Hopkins Hospital from March 2013 to December 2015. Patients in comas from different etiologies were monitored with NIRS within the first 12 to 24 hours of coma onset. All patients had an arterial line to measure MAP continuously. The protocol consisted of continuous monitoring for up to 3 days or until the patients had their arterial line removed. Monitoring could be repeated every week if patients had not awoken from the coma. All procedures received approval from The Johns Hopkins Medical Institutions Review Board.

NIRS-Based Autoregulation Monitoring

NIRS INVOS™ 5100 sensors (cerebral/somatic oximetry monitor, Covidien, Boulder, CO) were placed on the forehead of the patients. Analog arterial blood pressure signals were obtained from the bedside hemodynamic monitor and processed with a DT9800 data acquisition module (Data Translation Inc., Marlboro, MA). These signals and the raw digital NIRS signals were analyzed with ICM+ software (University of Cambridge, Cambridge, UK) as described previously [11]. Arterial blood pressure and NIRS signals were filtered to focus on the frequency of slow vasogenic waves, which mediate CA. The signals were filtered as non-overlapping 10-second mean values that were time-integrated, which is equivalent to having a moving average filter with a 10-second time window and resampling at 0.1 Hz, eliminating high-frequency components from respiration and pulse waveforms. Since both right and left forehead values of rScO₂ reproducibly demonstrated tight correlation ($R = 0.57$ to 0.68 , $P < 0.001$), we integrated single side measures into our equation to determine the upper and lower limits of autoregulation.

Fitting the Plateau, Lower and Upper Limits of the CA Curve

Individual CA curves (rScO₂ versus MAP) were constructed using Stata software version 13.0 (Stata Corp, College Station, TX) with data extracted from ICM+ software (University of Cambridge, Cambridge, UK)[12] considering a time window of 24 hours (MAP signals were sampled with an analogue-to-digital converter at 60 Hz). The MAP measurements were placed into 1 mmHg bins, which enabled us to observe the variance of rScO₂ in detail. In patients with more than one window period (> 24 hours) we were able to generate more than one curve. The 24-hour periods were selected randomly (we move the interval of time one-by-one hour trying to look for an autoregulation curve). We report all the CA curves, even the ones that did not have a visually apparent plateau, nor upper and lower limits of CA.

Statistical Analysis and Graph Construction

Descriptive characteristics of the individuals included in this study were analyzed with the statistical software Stata version 13.0 (Stata Corp, College Station, TX). The graphics were created by using the local polynomial smoothed line with 95% confidence intervals, as described in detail by Saleem et al. [10].

RESULTS

Autoregulation curves (identifiable plateau and upper or lower limits of CA) were identified in seven of the 33 patients who were monitored. Three patients were excluded as they were monitored less than 20 hours. The CA curves of the 30 patients are shown in the supplemental file. The seven patients whose CA curve was identified had a median monitoring duration of 43 hours (interquartile range [IQR]: 24–48 hours). The duration of monitoring was shorter for the remaining group of patients in whom the CA curves were not completely delineated, with a median of 34 hours, IQR [20 – 47]. Figure 1 shows the consistency between the plotted autoregulation curve and the range of optimal MAP according to the Aries method, an accepted technique to calculate optimal MAP using a parabolic curve derived from a graph that compares MAP versus cerebral oximetry index

(COx).[13] The patient highlighted in figure 1 had a large intracerebral hemorrhage (150cc volume) on the left frontal lobe with subfalcine herniation to the right.

We were able to plot the CA only in seven out of 30 patients for several reasons, including: i) the group with no identifiable ideal CA curve had a shorter duration of monitoring, which may not allow for spontaneous fluctuations of MAP to delineate the CA curve; ii) the MAP was not manipulated to plot the CA curve, only spontaneous fluctuations were observed; iii) other metabolic changes that affect rScO₂ measurements may have occurred (i.e. seizures, systemic hypoxemia); iv) frontal lobe lesions could have affected rScO₂ readings; v) some patients were dysregulated and had just a steep curve, indicating impaired CA.

We found different limits of autoregulation in the seven patients (See curves highlighted on yellow in supplemental file). When the autoregulation curves were plotted, the median lower and upper limits of autoregulation were 86.5 mmHg (IQR, 74-93.5) and 93.5 mmHg (IQR, 83-99), respectively. The plateau (difference between the limits of autoregulation) ranged from 4 to 17 mmHg.

With data from the case on Figure 2, we were able to plot two CA curves capturing dynamic changes on the plateau during the ICU stay. This patient was a 52-year-old woman with a high grade aneurysmal subarachnoid hemorrhage from a ruptured left posterior inferior cerebellar artery aneurysm that was surgically clipped. The autoregulation curve at the first day of monitoring is illustrated in Figure 2A. After 15 days, the patient developed cerebral vasospasm in the left posterior inferior cerebellar, basilar, and left posterior cerebral arteries confirmed with computed tomography angiography and magnetic resonance angiography. On the CA monitoring it was observed that the autoregulation curve had moved to the right, with higher lower and upper limits of CA (Figure 2B). The patient never had intracranial hypertension during the monitoring period; the highest intracranial pressure during monitoring was 15 mm Hg. The curves of the remaining patients are in the Supplementary file, including table 1 with the patient's demographics.

DISCUSSION

Our findings provide important information regarding the feasibility of delineating real trends of the CA plateau and direct visualization of the CA curve after at least 24 hours of recording without manipulation of MAP by external stimuli. The integration of multimodal monitoring at the bedside with cerebral oximetry provides a novel, noninvasive method to delineate daily individual CA curves.

Autoregulation curve were demonstrated decades ago in nonhuman subjects exposed to experimental stimuli to change the CPP.[7] In 2007, Brady et al. [8] demonstrated in a laboratory experiment in piglets that individualized autoregulation curves could be determined by comparing changes rScO₂ in response to variations of CPP. More recently, Budohoski et al. [9] and Saleem et al. [10] developed autoregulation curves that compared transcranial Doppler-derived cerebral blood flow velocity and MAP in humans. In our study, we were able to model autoregulation curves using rScO₂ and MAP in comatose adults in a Neurocritical Care Unit. Moreover, we demonstrated feasibility of observing autoregulation

plateau in humans without inducing experimental changes in MAP. Interestingly, we showed the evolution of the autoregulation curve in a patient with aneurysmal subarachnoid hemorrhage who developed cerebral vasospasm.

For many years the wide range of MAP (50–150 mmHg) mostly derived from experimental studies in animals was established as the safe range for autoregulation pressure in humans. [7] Now, recent studies supports the association between individualized autoregulation pressure and better functional outcomes.[14–16] Aries et al. [13], in a cohort of 327 patients with severe traumatic brain injury, observed that patients with a median CPP close to optimal CPP defined by CA monitoring were more likely to have a favorable outcome than those in whom median CPP was widely different from optimal CPP. Furthermore, evidence supports physiologic variability of autoregulation limits among critically ill patients. [7, 10]

We must emphasize that the methodology used in this study is dynamic autoregulation, whereas Lassen used static autoregulation.[7] Furthermore, Lassen measured CPP to plot the CA curve, but we measured MAP in order to use a non-invasive technique. MAP does not equal CPP when ICP is >0 , which is frequently the case in patients with acute intracranial injury and, as a result, the CA curve plotted with MAP will be shifted to the right on the X axes. Lassen plotted the CA curve measuring CBF and, in contrast, we are measuring rScO₂, which is only a surrogate of CBF. Measured rScO₂ can be altered by other physiologic variables, such as cardiac output, pulmonary function, systemic hypoxemia, acid-base status and PaCO₂, all of which affect not only the hemoglobin saturation for a given pO₂, but also cerebral blood flow.[17]

The rationale of using NIRS to monitor cerebral autoregulation is based on the assumption that the brain's oxygen content is positively related to arterial oxygen saturation, CBF, and oxygen-tissue diffusivity and negatively associated with the cerebral metabolic rate for oxygen. Comparisons of changes in tissue oxygenation over short periods of time (3–6 min) that occur in response to changes in MAP with presumed stable arterial saturation, stable metabolism, and stable diffusivity should give similar information to the comparison of changes in CBF and MAP.[18] While there is correlation between rScO₂ and CBF during changes in cerebral physiology, the values may differ as rScO₂ is calculated from the ratio between oxygenated and total hemoglobin (oxygenated and deoxygenated) from arteries, veins and capillaries and therefore can be altered by changes both in oxygen supply (e.g. CBF, oxygen supply), oxygen demand (cerebral metabolic rate) and possibly frontal lesions. In a study comparing rScO₂ from NIRS to functional MRI, Alderliesten et al.[19] nonetheless found an excellent correlation between rScO₂ from NIRS and CBF (Spearman 0.85, $p=0.00001$) measured by functional MRI during hypercapnia challenge in 7 healthy volunteers. The authors concluded that the use of NIRS rScO₂ as a biomarker for changes in cerebral hemodynamics appeared justified.

We did observe variability of rScO₂ between calculated optimal CA pressure time epochs, even within the same patient. Such observations emphasize the complexity of understanding a physiologic variable (rScO₂ NIRS) that is dependent on numerous physiologic variables (systemic oxygenation, volume resuscitation, CBF, CMRO₂). As an example, figure 1 highlights a patient whose right cortex was suffering left-to-right subfalcine herniation from

a large intracerebral hemorrhage (150cc volume) within the left frontal lobe. Low regional levels of rScO₂ were observed, and possibly reflect a mix of normal, low- and non-perfused tissue within the NIRS-perfused rScO₂ region. Despite the low rScO₂, we were able to plot a CA curve. The clinical example of aneurysmal SAH patient (figure 2) also demonstrated poor correlation between regional oxygen saturation and calculated optimal blood pressure. The autoregulatory curve has shifted to the right, as may be predicted by vascular spasm, while at that time rScO₂ had risen from the pre-vasospasm period. The increase in rScO₂ plateau would be consistent with several underlying mechanisms: 1) relative hyperemia via greater CBF (vasospasm therapy); 2) underlying hypo-metabolism (ischemic/infarction); 3) combination of points 1 & 2.

These data provide an important tenet; we cannot presume that depressed NIRS-derived rScO₂ translates to “need more oxygen or CBF”, or that a “high” rScO₂ implies “safe perfusion level”. Rather we can and should target “best perfusion pressure” as the best monitoring variable since rScO₂ has such complexity in understanding regional physiologic state.

This case-series study has important limitations. First, the cause of coma in this study population included many different etiologies, which may explain the variations in plateau ranges. However, we intentionally used a diverse population to be able to generalize the applicability of this methodology. Second, the ranges of autoregulation were calculated visually from the curves, thus limiting the accuracy of our analysis. Third, the small sample size limits our conclusions. Lastly, we were only able to identify the CA curves in a small number of patients (7 of 30). This low rate is likely due to the shorter duration of monitoring (<24 hours) for 12 of the 30 patients and the fact that we did not manipulate MAP.

CONCLUSIONS

This case-series study showed feasibility of delineating real trends of the CA plateau and direct visualization of the CA curve after at least 24 hours of recording without manipulation of MAP by external stimuli. The integration of multimodal monitoring at the bedside with cerebral oximetry provides a novel, noninvasive method to delineate daily individual CA curves. Future studies are needed to explore the further the feasibility and effectiveness of using this technique in a larger cohort of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Autoregulation curve created with the ICM+ software illustrating the autoregulatory plateau that is consistent with the nadir of the parabola derived from the Aries' method. [13] The patient had a large intracerebral hemorrhage (150cc volume) on the left frontal lobe with subfalcine herniation from left to right. ABP, mean arterial blood pressure; Cox right, cerebral oximetry index from the right side; rSO₂R, regional cerebral oxygen saturation from the right side.

Figure 2.

Autoregulation curves for a patient with aneurysmal subarachnoid hemorrhage. (A) Autoregulation curve on day 1 without cerebral vasospasm; the lower autoregulatory threshold is 70 mmHg and the upper threshold is 80 mmHg. (B) Autoregulation curve 15 days later when cerebral vasospasm occurred. Note how the curve moved to the right, the lower threshold increased to 90 mmHg, and the upper threshold increased to 100 mmHg.