Assessment of Cerebral Autoregulation Patterns with Near-infrared Spectroscopy during Pharmacological-induced Pressure Changes

Annelies T. Moerman, M.D., Ph.D., Valerie M. Vanbiervliet, M.D., Astrid Van Wesemael, M.D., Stefaan M. Bouchez, M.D., Patrick F. Wouters, M.D., Ph.D., Stefan G. De Hert, M.D., PhD.

ABSTRACT

Background: Previous work has demonstrated paradoxical increases in cerebral oxygen saturation (S_cO_2) as blood pressure decreases and paradoxical decreases in S_cO_2 as blood pressure increases. It has been suggested that these paradoxical responses indicate a functional cerebral autoregulation mechanism. Accordingly, the authors hypothesized that if this suggestion is correct, paradoxical responses will occur exclusively in patients with intact cerebral autoregulation.

Methods: Thirty-four patients undergoing elective cardiac surgery were included. Cerebral autoregulation was assessed with the near-infrared spectroscopy–derived cerebral oximetry index (COx), computed by calculating the Spearman correlation coefficient between mean arterial pressure and S_cO_2. COx less than 0.30 was previously defined as functional autoregulation. During cardiopulmonary bypass, 20% change in blood pressure was accomplished with the use of nitroprusside for decreasing pressure and phenylephrine for increasing pressure. Effects on COx were assessed. Data were analyzed using two-way ANOVA, Kruskal–Wallis test, and Wilcoxon and Mann–Whitney U test.

Results: Sixty-five percent of patients had a baseline COx less than 0.30, indicating functional baseline autoregulation. In 50% of these patients (n = 10), COx became highly negative after vasoactive drug administration (from −0.04 [−0.25 to 0.16] to −0.63 [−0.83 to −0.26] after administration of phenylephrine, and from −0.05 [−0.19 to 0.17] to −0.55 [−0.94 to −0.35] after administration of nitroprusside). A negative COx implies a decrease in S_cO_2 with increase in pressure and, conversely, an increase in S_cO_2 with decrease in pressure.

Conclusions: In this study, paradoxical changes in S_cO_2 after pharmacological-induced pressure changes occurred exclusively in patients with intact cerebral autoregulation, corroborating the hypothesis that these paradoxical responses might be attributable to a functional cerebral autoregulation. **(Anesthesiology 2015; 123:327-35)**

A NUMBER of recent reports using near-infrared spectroscopy (NIRS) for monitoring of cerebral oxygen saturation (S_cO_2) observed paradoxical changes in S_cO_2 in response to changes in blood pressure. Decreases in blood pressure after administration of sodium nitroprusside (SNP) were associated with increases in S_cO_2,[1,2] and likewise, S_cO_2 decreased after administration of phenylephrine, despite an increase in blood pressure.[1–7]

For some authors, this observation was reason to question the validity of the NIRS technology,[2] whereas others instead concluded that the paradoxical reactions should prompt revision of the current concept of cerebral autoregulation.[8] Indeed, on the basis of the classic concept of autoregulation, one would expect an autoregulatory plateau where cerebral blood flow (CBF) and S_cO_2 remain stable between mean arterial pressures (MAPs) of 50 and 150 mmHg, and concomitant parallel changes in S_cO_2 and blood pressure occur when the upper and lower limits of autoregulation are exceeded. The observed paradoxical reactions, where S_cO_2 and blood pressures change in opposite directions, do not fit into this classic concept of cerebral autoregulation.

What We Already Know about This Topic

- Vasoactive medication might evoke paradoxical changes in cerebral oxygen saturation with blood pressure changes
- These data do not fit into the classic concept of cerebral autoregulation, which has been grounded in older literature

What This Article Tells Us That Is New

- Paradoxical reactions might be part of a normal physiological autoregulatory response, thereby challenging the conventional paradigm
- Intact cerebral autoregulation comprises additional patterns of normal cerebrovascular responses that might be obscured if the existence of different mechanisms is ignored and analysis is based on the mean response of a group

It was hypothesized that these paradoxical reactions are attributable to a functional cerebral autoregulation mechanism.[6–8] The abrupt changes in perfusion pressure are supposed to provoke changes in resistance in the cerebral

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autoregulatory arterioles, arteriolar vasoconstriction when pressure increases,[6,7] and arteriolar vasodilation when pressure decreases.[8,9] The resultant change in arterial to venous blood volume ratio would then explain the change in S_cO_2.[6,7] Therefore, it seems that cerebral autoregulation, which has so far been considered as one physiological entity, may in fact comprise additional physiological responses that have been underreported to date.[8]

Cerebral autoregulation is a complex physiological phenomenon, and a quantitative definitive standard measure of cerebral autoregulation is lacking. Therefore, the suggestion that paradoxical reactions are attributable to a functional pressure autoregulation mechanism remains hypothetical.

In this study, data from a previous experiment measuring S_cO_2 with NIRS during pharmacologic-induced pressure changes[1] were used to identify the type of S_cO_2 response to pressure change (normal or paradoxical). Our hypothesis was that if paradoxical changes in S_cO_2 indicate a functional cerebral autoregulation mechanism, as previously suggested,[6–8] these paradoxical reactions will occur exclusively in patients with an intact cerebral autoregulation mechanism. If this hypothesis proves to be correct, this would imply that intact cerebral autoregulation constitutes of additional patterns of normal cerebrovascular responses than described so far.

Materials and Methods

Data were prospectively collected during a clinical study evaluating the effects of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation. These data have been previously reported.[1] We retrospectively calculated the cerebral oximetry index (COx) from these data.

The study was approved by the institutional ethics committee (Ethics Committee Ghent University Hospital, Gent, Belgium), and written informed consent was obtained from all subjects. The initial trial was registered at ClinicalTrials.gov (NCT01424800).

Thirty-four adult patients scheduled for elective cardiac surgery (coronary artery bypass grafting and/or valve surgery) on moderately hypothermic cardiopulmonary bypass (CPB) without blood transfusion were recruited. Patients with history of cerebrovascular disease or significant carotid artery stenosis (greater than 60%) and patients necessitating vasopressor or inotropic therapy before surgery were excluded.

On the morning of surgery, patients were allowed to take their routine medication, except angiotensin-converting enzyme inhibitors. Patients were premedicated with oral diazepam (5 to 10 mg). Standard monitoring was used throughout the procedure, including electrocardiograph, pulse oximetry, end-tidal oxygen, carbon dioxide and sevoflurane concentrations, bispectral index (BIS), invasive arterial and central venous pressure measurement, and temperature measurement (AS3, Datex, Finland). Arterial blood pressure was recorded continuously through the right radial artery catheter. Two disposable NIRS sensors were applied on each side of the forehead for continuous registration of S_cO_2 of the corresponding brain hemisphere (INVOS 5100C, Covidien, U.S.A.). S_cO_2 recording started while the patients breathed room air. All data were recorded continuously and integrated digitally (except BIS) with the RUGLOOP® software (Demed, Belgium).

Anesthesia was induced with fentanyl 5 μg/kg, diazepam 0.1 mg/kg, and rocuronium 1 mg/kg. The lungs were ventilated mechanically with oxygen-enriched air (fractional inspired oxygen, 0.6) adjusted to keep the end-tidal CO_2 around 40 mmHg. Anesthesia was maintained with boluses of fentanyl up to a total dose of 25 to 35 μg/kg and sevoflurane to maintain BIS values between 40 and 50.

CPB was performed with a roller pump (Stöckert S5; Sorin group Deutschland GmbH, Germany) providing nonpulsatile flow. The priming consisted of 1,200 ml colloids (Geloplasma®, Fresenius Kabi, Belgium), heparin 5,000 IU, and mannitol 0.5 g/kg. Systemic heparinization maintained an activated clotting time of more than 480 s. Moderately hypothermic CPB (blood temperature, 30°C) was initiated at flow rates of 2.5 $l \cdot min^{-1} \cdot m^{-2}$. During CPB, Pa_{O_2} and Pa_{CO_2} were maintained around 200 and 40 mmHg, respectively. Arterial blood gases were measured at 37°C, independent of body temperature (α-stat blood gas management). Blood was sampled from the pump oxygenator after 3 min during steady state and during the interventions. Temperature, Pa_{CO_2}, Pa_{O_2}, hemoglobin, and sevoflurane concentrations were kept constant during the respective measurements.

Interventions

The study used a randomized crossover design where the subjects served as their own controls. Methodology has been previously described in detail.[1] In brief, 20% changes in perfusion pressure during CPB were generated with the use of vasoactive agents, SNP for decreasing blood pressure and phenylephrine for increasing blood pressure. The vasoactive agents are part of the standard of care, and preparation and labeling were conducted according to the hospital guidelines (250 and 100 μg/ml for SNP and phenylephrine, respectively). The protocol of the previous study[1] included a decrease in flow rate of 20% before administration of phenylephrine, whereas flow rate was 2.5 $l \cdot min^{-1} \cdot m^{-2}$ before administration of SNP.

First, flow rate was set to the respective target. Thereafter, steady state was established. Steady state was defined as the presence of a stable (less than 10% change) perfusion pressure over a period of 5 min on CPB. No changes in any parameters (temperature, Pa_{CO_2}, Pa_{O_2}, sevoflurane concentrations, and flow rate) nor administration of any drugs were allowed during steady state. After reaching 5 min of steady state, 20% change in perfusion pressure was induced. The pressure changes were sustained for 5 min by administration of small boluses of the respective drugs.

Outcome Variables

Data were sampled at 2-s intervals with RUGLOOP®, stored on a computer hard drive, and analyzed offline. Because there were no significant differences in S_cO_2 between the left and the right side among the different interventions, right and left S_cO_2 were averaged to analyze changes in S_cO_2.

Cerebral autoregulation was quantified using the NIRS-derived COx.[10–18] COx was calculated by recording 2-s values of MAP and S_cO_2 over a 300-s epoch, generating 150 paired samples of MAP and S_cO_2 to calculate the correlation coefficient between MAP and S_cO_2. Traditionally, signal filtering has been performed by using 10-s average values to eliminate confounding variables such as respiration and pulse waveforms.[11,16] Because in this study, measurements were performed on CPB, potential influences of respiration and pulse waveforms are absent, and therefore, there was no need for data filtering. Moreover, in view of the abrupt deliberate pressure changes, the use of 2-s samples was considered more accurate than 10-s averaged values.

Blood pressure in the autoregulation range is indicated by a COx that approaches 0, whereas a COx approaching +1 indicates a pressure passive cerebral circulation.[10–14] The COx thresholds to distinguish between intact and impaired autoregulation are arbitrary and vary according to the authors between 0.25 and 0.50.[11,12,14–16] In this study, the arbitrary limit of 0.30 was chosen, according to the most recent work of Ono *et al.*[14,19]

Statistical Analysis

This study was performed with data that were consecutively recorded for a different project published previously,[1] and thus, the initial sample size was not powered to relate paradoxical responses of S_cO_2 to cerebral autoregulation. Currently, no data are available in literature to allow for the calculation of sample size when changes in cerebral autoregulation are to be related to the use of vasoactive agents. Therefore, we consider this study as a pilot study to evaluate the impact of vasoactive agents on COx. This study will allow to further tailor future sample size calculations.

Statistical analysis was performed using the statistical software SPSS Statistics 22 (SPSS Inc., U.S.A.). Distribution of the data was tested for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD. Nonparametric data are presented as median (range). Spearman correlation coefficient was used to determine the COx. Comparisons of COx values, whether the intervention started with phenylephrine or SNP, were made with Mann–Whitney U test. The changes in COx were evaluated with the Wilcoxon signed-rank test. Drug doses were analyzed with the Kruskal–Wallis test. Differences in drug doses among the different groups were examined for significance by using Mann–Whitney U test. Two-way repeated measures ANOVA was used to assess the group and intervention main effect, as well as the group × intervention interaction. Bonferroni test was chosen to correct for multiple comparisons. *P* value less than 0.05 was taken as the level of significance.

Results

The flow diagram for the enrolment, study inclusion, and data analysis is presented in figure 1. Nine women and 25 men with an average age of 62 ± 14 yr, weight of 80 ± 16 kg, and height of 171 ± 9 cm were enrolled in the study. All patients were included in the SNP trial (n = 34), while three patients were excluded from the phenylephrine trial (n = 31) because blood pressure at the intended start of the pressure increasing intervention was considered too high to accept a deliberate further increase (fig. 1).

There were no differences between the COx data whether the intervention started with phenylephrine or with SNP; therefore, data from both groups were pooled for analysis (table 1). When all patients were analyzed together, administration of phenylephrine (n = 31) induced a significant change in COx values (median [range], from 0.13 [−0.20 to 0.79] to −0.26 [−0.83 to 0.84], $P < 0.001$). After administration of SNP (n = 34), COx values did not change significantly (from 0.11 [−0.20 to 0.79] to 0.32 [−0.94 to 0.93], $P = 0.12$). Considering the classic concept of autoregulation, and with arbitrary COx thresholds to distinguish between intact and impaired autoregulation that range between 0.25 and 0.50,[11,12,14–16] this means that all patients can be considered to have a normal cerebral autoregulation, both at baseline and after administration of vasoactive agents. However, looking at the individual responses, a different picture becomes apparent.

The different autoregulatory patterns when intersubject variations were considered are presented in figure 2. Twelve patients (35%) had a baseline COx more than 0.30, implying that changes in blood pressure are associated with parallel changes in S_cO_2, *i.e.*, the cerebral circulation is pressure passive. Sixty-five percent of patients (n = 22) had a baseline COx less than 0.30, indicating functional cerebral autoregulation.

According to the effect of pressure changes on COx, four different patterns could be discriminated:

1. Pressure passive cerebral circulation (group 1 in fig. 2) (n = 12)

In all patients with baseline COx more than 0.30, COx remained more than 0.30 after administration of phenylephrine and SNP (COx: median [range], from 0.55 [0.24 to 0.79] to 0.53 [0.41 to 0.84] for phenylephrine, and from 0.64 [0.40 to 0.77] to 0.54 [0.35 to 0.93] for SNP), indicating that the cerebral circulation remained pressure passive after vasoactive drug administration.

2. Classic pattern of autoregulation (group 2 in fig. 2) (n = 6)

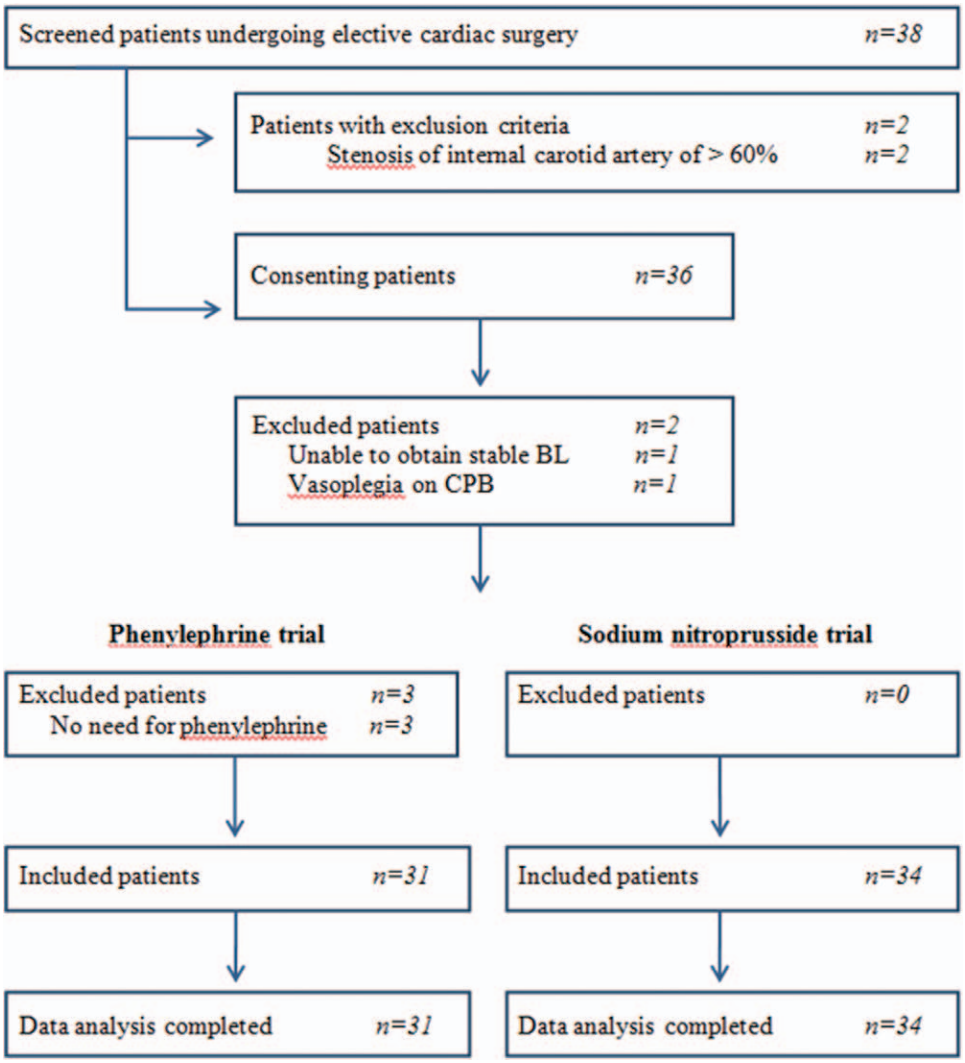

Fig. 1. Flow chart presenting the enrolment, study inclusion, and data analysis. BL = baseline; CPB = cardiopulmonary bypass.

Table 1. Median COx Values at Baseline and during the Respective Interventions, Demonstrating No Differences whether the Intervention Started with Phenylephrine or Sodium Nitroprusside

	PEBLCOx	PECOx	SNPBLCOx	SNPCOx
First PE (n = 15)	0.10 (–0.20 to 0.79)	–0.33 (–0.83 to 0.53)	0.13 (–0.18 to 0.77)	0.28 (–0.94 to 0.81)
First SNP (n = 19)	0.22 (–0.25 to 0.68)	0.20 (–0.65 to 0.84)	0.17 (–0.19 to 0.71)	0.36 (–0.93 to 0.93)
P value	0.61	0.14	0.56	0.34

Data are expressed as median (range).

COx = cerebral oximetry index; PE = phenylephrine; PEBLCOx = baseline cerebral oximetry index before administration of phenylephrine; PECOx = cerebral oximetry index after administration of phenylephrine; SNP = sodium nitroprusside; SNPBLCOx = baseline cerebral oximetry index before administration of sodium nitroprusside; SNPCOx = cerebral oximetry index after administration of sodium nitroprusside.

In six patients with intact baseline autoregulation, the classic pattern of autoregulation was observed. COx approached 0 at baseline and remained around 0 after administration of vasoactive agents, indicating that the patients were on the autoregulatory plateau (from 0.04 [–0.11 to 0.21] to –0.01 [–0.36 to 0.02] for phenylephrine, and from 0.01 [–0.18 to 0.12] to 0.015 [–0.07 to 0.28] for SNP).

3. Paradoxical changes in S_cO_2 after administration of phenylephrine or SNP (group 3 in fig. 2) (n = 10)

In 10 patients with intact baseline autoregulation, COx became highly negative after administration of phenylephrine or SNP (from –0.04 [–0.25 to 0.16] to –0.63 [–0.83 to –0.26] for phenylephrine, and from –0.05 [–0.19 to 0.17] to –0.55 [–0.94 to –0.35] for SNP). A negative COx implies a

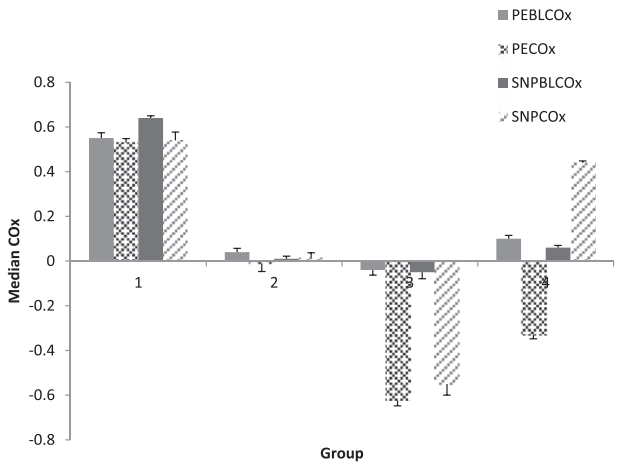

Fig. 2. Median COx values at baseline and after administration of phenylephrine and sodium nitroprusside. COx = cerebral oximetry index; Group 1 = pressure passive cerebral circulation; Group 2 = classic pattern of autoregulation; Group 3 = paradoxical S_cO_2 changes after vasoactive drug administration; Group 4 = divergent effects of phenylephrine and sodium nitroprusside on COx. PEBLCOx = baseline cerebral oximetry index before administration of phenylephrine; PECOx = cerebral oximetry index after administration of phenylephrine; SNPBLCOx = baseline cerebral oximetry index before administration of sodium nitroprusside; SNPCOx = cerebral oximetry index after administration of sodium nitroprusside.

paradoxical decrease in S_cO_2 with phenylephrine-induced increase in blood pressure, and *vice versa*, a paradoxical increase in S_cO_2 with SNP-induced decrease in blood pressure.

4. Divergent effects of phenylephrine and SNP on COx (group 4 in fig. 2) (n = 6)

In six patients with intact baseline autoregulation, COx became negative after administration of phenylephrine (from 0.10 [−0.13 to 0.20] to −0.33 [−0.40 to −0.06]), whereas COx increased to more than 0.30 after administration of SNP (from 0.06 [−0.06 to 0.23] to 0.44 [0.32 to 0.53]). This indicates that in both interventions, S_cO_2 decreased. So S_cO_2 decreased when blood pressure decreased with SNP, but S_cO_2 also decreased when blood pressure increased with phenylephrine (resulting in a positive and negative COx, respectively).

Patient characteristics and drug doses for the four groups are presented in table 2. There were no differences between the four groups. The intraoperative data for the 4 groups at baseline and during the respective interventions are presented in table 3. During the phenylephrine trial, temperature was significantly lower ($P = 0.02$) and $Paco_2$ was significantly higher ($P = 0.03$) in group 1 compared with group 3; and sevoflurane concentration was significantly higher in group 1 compared with group 4 ($P = 0.03$).

Discussion

In this study, we tested the hypothesis that paradoxical increases in S_cO_2 as blood pressure decreases and paradoxical decreases in S_cO_2 as blood pressure increases indicates a functional cerebral autoregulation mechanism. Our results demonstrate that paradoxical changes occurred exclusively in patients with intact cerebral autoregulation, supporting this hypothesis. We also observed substantial intersubject variations in the response to pharmacologic-induced pressure changes. This implies that the relation between MAP and S_cO_2 may follow different patterns and that intact cerebral autoregulation may manifest not only as an autoregulatory plateau but also as a paradoxical response. Interestingly, Jones *et al.*[8] demonstrated that when individual autoregulation curves are averaged together, the classic pattern results. This is confirmed in the current work, where the different autoregulatory patterns were obscured when analysis was based on group means. This underscores the risk of bias that may occur in the interpretation of data when the existence of different mechanisms is ignored.

Four different autoregulatory patterns were observed when pharmacological changes in perfusion pressure were induced (fig. 2).

1. Pressure passive cerebral circulation (35%)

Thirty-five percent of patients had a baseline COx more than 0.30, remaining more than 0.30 after administration of vasoactive drugs. COx more than 0.30 implies that changes in blood pressure are associated with parallel changes in S_cO_2, *i.e.*, the cerebral circulation is pressure passive. The

Table 2. Patient Characteristics and Drug Doses for the Four Groups

	Group 1 (n = 12)	Group 2 (n = 6)	Group 3 (n = 10)	Group 4 (n = 6)	*P* Value
Age (yr)	58 ± 18	69 ± 11	63 ± 12	60 ± 13	0.48
Weight (kg)	81 ± 20	79 ± 21	79 ± 7	79 ± 18	0.98
Height (cm)	173 ± 11	172 ± 10	168 ± 7	170 ± 9	0.66
MAP awake (mmHg)	99 ± 18	100 ± 8	97 ± 13	86 ± 3	0.18
Left S_cO_2 awake (%)	65 ± 6	67 ± 3	65 ± 11	69 ± 3	0.72
Right S_cO_2 awake (%)	68 ± 8	67 ± 5	62 ± 8	70 ± 4	0.18
Dose SNP (μg)	137.5 (50–375)	87.5 (25–150)	400 (100–675)	125 (25–250)	0.08
Dose PE (μg)	175 (150–600)	50 (10–400)	150 (20–300)	50 (50–600)	0.17

Data are expressed as mean ± SD or median (range).

Awake = while breathing room air; Group 1 = pressure passive cerebral circulation; Group 2 = classic pattern of autoregulation; Group 3 = paradoxical S_cO_2 changes after vasoactive drug administration; Group 4 = divergent effects of phenylephrine and SNP on cerebral oximetry index; MAP = mean arterial blood pressure; PE = phenylephrine; S_cO_2 = cerebral oxygen saturation; SNP = sodium nitroprusside.

Table 3. Mean Intraoperative Data for the Four Groups at Baseline and during the Interventions

	Group 1 (n = 12)	Group 2 (n = 6)	Group 3 (n = 10)	Group 4 (n = 6)	*P* Value between Groups	*P* Value between Interventions	*P* Value (Group × Intervention Interaction)
MAP (mmHg)					0.70	< 0.001	0.21
PEBL	59 ± 12	59 ± 7	56 ± 9	55 ± 10			
PE	69 ± 9	70 ± 9	75 ± 6	67 ± 8			
SNPBL	68 ± 6	67 ± 6	70 ± 10	62 ± 6			
SNP	54 ± 8	54 ± 7	60 ± 8	52 ± 8			
Flow (l/min)					0.98	< 0.001	0.87
PEBL	3.6 ± 0.4	3.7 ± 0.4	3.5 ± 0.2	3.6 ± 0.6			
PE	3.6 ± 0.4	3.8 ± 0.4	3.6 ± 0.3	3.7 ± 0.4			
SNPBL	4.4 ± 0.5	4.5 ± 0.7	4.5 ± 0.3	4.5 ± 0.5			
SNP	4.4 ± 0.5	4.5 ± 0.7	4.5 ± 0.3	4.5 ± 0.5			
Blood temperature (°C)					0.02	0.15	0.32
PEBL	29.5 ± 0.8	30.4 ± 1.7	31.2 ± 1.2	30.4 ± 1.3		*P* = 0.02; group 1 *vs.* 3	
PE	29.5 ± 0.8	31.0 ± 0.4	31.5 ± 1.2	30.9 ± 1.8			
SNPBL	29.7 ± 1.2	29.8 ± 1.3	30.8 ± 1.6	30.6 ± 1.5			
SNP	30.0 ± 1.2	30.0 ± 1.4	31.0 ± 1.2	31.0 ± 1.4			
Sevoflurane (%)					0.02	0.18	0.12
PEBL	1.7 ± 0.8	1.1 ± 0.3	1.3 ± 0.4	0.8 ± 0.2			
PE	1.6 ± 0.8	1.1 ± 0.4	1.3 ± 0.5	0.8 ± 0.2		*P* = 0.03, group 1 *vs.* 4	
SNPBL	1.1 ± 0.4	1.0 ± 0.2	1.3 ± 0.4	0.8 ± 0.2			
SNP	1.2 ± 0.6	1.0 ± 0.3	1.4 ± 0.4	0.8 ± 0.2			
pH					0.17	0.19	0.10
PEBL	7.37 ± 0.04	7.41 ± 0.03	7.41 ± 0.03	7.41 ± 0.03			
PE	7.37 ± 0.04	7.40 ± 0.01	7.41 ± 0.03	7.41 ± 0.03			
SNPBL	7.38 ± 0.03	7.40 ± 0.04	7.40 ± 0.04	7.40 ± 0.03			
SNP	7.39 ± 0.03	7.40 ± 0.04	7.40 ± 0.03	7.40 ± 0.03			
Pa_{O_2} (mmHg)					0.83	0.17	0.27
PEBL	211 ± 50	230 ± 56	224 ± 47	203 ± 42			
PE	211 ± 50	244 ± 50	224 ± 47	213 ± 38			
SNPBL	251 ± 67	246 ± 59	227 ± 55	216 ± 55			
SNP	211 ± 48	229 ± 51	210 ± 59	211 ± 46			
Pa_{CO_2} (mmHg)					0.03	0.13	0.14
PEBL	45 ± 4	41 ± 3	40 ± 3	39 ± 2			
PE	45 ± 4	42 ± 2	40 ± 3	40 ± 2		*P* = 0.03, group 1 *vs.* 3	
SNPBL	44 ± 3	42 ± 7	41 ± 4	42 ± 3			
SNP	43 ± 2	41 ± 5	41 ± 2	43 ± 4			
Hb (g/dl)					0.70	0.07	0.81
PEBL	10.1 ± 1.5	10.2 ± 1.3	9.6 ± 0.8	10.0 ± 0.9			
PE	10.1 ± 1.5	10.2 ± 0.9	9.6 ± 0.8	9.9 ± 1.2			
SNPBL	9.7 ± 1.4	9.6 ± 1.1	9.4 ± 1.0	10.0 ± 1.2			
SNP	9.8 ± 1.4	9.9 ± 1.2	9.6 ± 1.0	10.3 ± 1.2			

Data are expressed as mean ± SD.

Group 1 = pressure passive cerebral circulation; Group 2 = classic pattern of autoregulation; Group 3 = paradoxical S_cO_2 changes after vasoactive drug administration; Group 4 = divergent effects of phenylephrine and SNP on cerebral oximetry index; Hb = hemoglobin; MAP = mean arterial blood pressure; PE = phenylephrine; PEBL = baseline value before administration of phenylephrine; S_cO_2 = cerebral oxygen saturation; SNP = sodium nitroprusside; SNPBL = baseline value before administration of sodium nitroprusside.

observed incidence of 35% of pressure passive cerebral circulation conforms with previous studies[20] and reflects the high-risk population in cardiac surgery. Interestingly, in the patient group with COx more than 0.30, Pa_{CO_2} and sevoflurane concentrations were significantly higher and temperature was significantly lower compared with the patient group with paradoxical changes in S_cO_2 after administration of phenylephrine (groups 3 and 4). This despite the fact that in the study design[1] these variables were controlled within narrow limits. The finding in the current analysis that especially in these patients a pressure passive response was shown corroborates with results of previous studies, demonstrating that higher Pa_{CO_2},[7] high sevoflurane concentration,[21] and hypothermic CPB[20] are associated with impaired cerebral autoregulation.

2. Classic pattern of autoregulation (18%)

Interestingly, only 18% of all patients fulfilled the classic criteria of intact cerebral autoregulation. COx remained around 0 after administration of vasoactive agents, indicating that

S_cO_2 remained constant when blood pressure changed, so patients were on the autoregulatory plateau.

3. Paradoxical changes in S_cO_2 after administration of phenylephrine or SNP (29%)

In 10 patients with intact baseline autoregulation, COx became highly negative after administration of phenylephrine or SNP. A negative COx implies a paradoxical decrease in S_cO_2 with phenylephrine-induced increase in blood pressure and, *vice versa*, a paradoxical increase in S_cO_2 with SNP-induced decrease in blood pressure.

4. Divergent effects of phenylephrine and SNP on COx (18%)

In six patients with functional baseline autoregulation, S_cO_2 decreased after administration of both phenylephrine and SNP, resulting in a negative COx with phenylephrine and a positive COx with SNP. The negative COx after administration of phenylephrine should be considered as a paradoxical reaction, implying a decrease in S_cO_2 with an increase in blood pressure. The positive COx after administration of SNP indicates a parallel decrease in S_cO_2 with a decrease in blood pressure. Although not unequivocally clear, this observation might be attributed to a dose-dependent impairment of cerebral autoregulation with SNP[22,23] or it might just be the consequence of blood pressure crossing the lower limit of autoregulation.[10] Lower limits of autoregulation cannot be derived from the current analysis, and therefore the exact mechanism of this finding cannot be identified from the current study.

The mechanism of paradoxical reactions remains controversial. Although these reactions do not fit in the classic concept of autoregulation, some authors have suggested that instead these are specifically representative for the presence of a functional pressure autoregulation mechanism.[6–8] According to their theory, the phenylephrine-induced increase in perfusion pressure provokes vasoconstriction of the cerebral autoregulatory arterioles to prevent abrupt cerebral hyperperfusion. This causes a decreased arterial blood contribution to NIRS measurements, resulting in a lower S_cO_2.[6,7] The S_cO_2 increase with induced hypotension could be readily explained by the same mechanism. To prevent cerebral hypoperfusion, cerebral arterioles dilate,[8,9] increasing the arterial to venous blood volume ratio, and thereby increasing S_cO_2.

In an experimental study, Jones *et al.*[8] demonstrated a paradoxical increase in CBF during nonpharmacological-induced hypotension, which they characterized as an overcompensation of the autoregulatory mechanism. The authors hypothetized that to prevent abrupt cerebral perfusion changes, the cerebral autoregulatory vessels are reacting more than is necessary to maintain the autoregulatory plateau. They termed this phenomenon "hyperautoregulation." Recently, this phenomenon has also been described in a clinical study, evaluating the relationship between blood pressure and CBF in humans. An overshoot of the middle cerebral blood velocity was observed after a sit-to-stand trial, resulting in a negative correlation between blood pressure and CBF, for which the authors did not have a clear explanation.[24] We observed paradoxical changes in S_cO_2 in both increased and decreased perfusion pressure, only occurring in patients with intact baseline cerebral autoregulation, supporting this view on cerebral autoregulation.

Several methodological aspects of the study require attention. The lack of a valid methodology to quantify cerebral autoregulation makes advancing knowledge in this field extremely challenging. Recently, NIRS has been introduced as a method to evaluate cerebral autoregulation noninvasively. This approach presumes that S_cO_2 is a reliable surrogate of CBF,[11–13] which continues to be a point of discussion, despite the fact that NIRS as a method to evaluate cerebral autoregulation has been validated in numerous studies.[11,15–18,25] Especially when autoregulation is determined during rapid blood pressure changes induced by intravenous boluses of vasoactive agents, S_cO_2 changes other than those because of CBF changes (change in hemoglobin, temperature, and others) are considered to be negligible.[25]

Many regulating processes intercept at the level of cerebrovascular reactivity, making conclusions on underlying mechanisms extremely hazardous. However, we emphasize that the current analysis was not intended to identify the mechanisms for impaired regulation nor to determine causal relationships between COx more than 0.30 and risk factors for impaired autoregulation. In the current study, we demonstrated that paradoxical changes in S_cO_2 occur exclusively in patients with an intact autoregulation mechanism. We reason that if other causes such as direct pharmacological effects of the vasoactive agents, extracranial contamination of the NIRS signal,[26–30] or patient-related or intraoperative confounders would be accountable for the paradoxical reactions, those reactions would have occurred in every patient. The fact that we clearly demonstrated that paradoxical reactions only occurred in patients with intact autoregulation supports the hypothesis put forward by others that these paradoxical reactions might be part of a normal physiological autoregulation mechanism.

The results of the current study should be interpreted within the constraints of the methodology. First, NIRS measures oxygen saturation in a superficial area of the brain directly below the sensors but does not examine the whole brain. It is possible that there might be heterogeneity of autoregulatory patterns in the brain and that the patterns that are observed in the cerebral cortex cannot be extrapolated to the whole brain.[8]

Second, phenylephrine and SNP were administered in bolus, not in continuous infusion. The precipitous changes in pressure caused by bolus administration presumably might elicit autoregulatory reactions, which would not be seen with gradual changes in pressure. Tzeng *et al.*[24] demonstrated that CBF dynamics are driven by the rate of change in blood pressure rather than absolute pressure *per se*.

A comparison study between bolus and infusion would be informative in this regard.

Third, in line with the previously mentioned studies,[10–17,19,20] we evaluated the concordance between MAP and S_cO_2 using simple correlation analysis. However, cerebral autoregulation is a complex physiological system, and it could be argued that correlation analysis does not cope with the complex interplay and the time-varying aspects of the different physiological mechanisms.[31] Coherence and transfer function analyses have also been used to quantify cerebral autoregulation.[32,33] Caicedo *et al.* analyzed four different measurement models used for cerebral autoregulation assessment (correlation, coherence, modified coherence, and transfer function). Although Caicedo *et al.*[34] proposed transfer function gain as the most robust method when used for cerebral autoregulation studies, correlation was also considered as a robust method, despite some time delay–related restrictions.

Perspectives and Significance

Our observations suggest that the classic description of autoregulation might represent only part of the picture. Consistent with many scattered data of paradoxical increases in S_cO_2 as blood pressure decreases and paradoxical decreases in S_cO_2 as blood pressure increases, the current study supports the hypothesis that these paradoxical reactions might be part of a normal physiological autoregulatory response.

The differences in autoregulatory patterns have direct implications for definitions of blood pressure targets and for perioperative hemodynamic management. Individualizing arterial blood pressure targets based on cerebral autoregulation monitoring may provide a more effective means for preventing cerebral hyperperfusion and hypoperfusion than the current standard of care.

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Competing Interests

Dr. Moerman received lecture fees from Covidien AG, Neuhausen am Rheinfall, Switzerland. All other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Moerman: Department of Anesthesiology, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium. annelies.moerman@ugent.be. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Moerman A, Denys W, De Somer F, Wouters PF, De Hert SG: Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. Br J Anaesth 2013; 111:619–26
2. Lucas SJ, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN: Influence of changes in blood pressure on cerebral perfusion and oxygenation. Hypertension 2010; 55:698–705
3. Meng L, Cannesson M, Alexander BS, Yu Z, Kain ZN, Cerussi AE, Tromberg BJ, Mantulin WW: Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth 2011; 107:209–17
4. Nissen P, Brassard P, Jørgensen TB, Secher NH: Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care 2010; 12:17–23
5. Brassard P, Seifert T, Wissenberg M, Jensen PM, Hansen CK, Secher NH: Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. J Appl Physiol 2010; 108:1472–8
6. Ogoh S, Sato K, Fisher JP, Seifert T, Overgaard M, Secher NH: The effect of phenylephrine on arterial and venous cerebral blood flow in healthy subjects. Clin Physiol Funct Imaging 2011; 31:445–51
7. Meng L, Gelb AW, Alexander BS, Cerussi AE, Tromberg BJ, Yu Z, Mantulin WW: Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. Br J Anaesth 2012; 108:815–22
8. Jones SC, Radinsky CR, Furlan AJ, Chyatte D, Qu Y, Easley KA, Perez-Trepichio AD: Variability in the magnitude of the cerebral blood flow response and the shape of the cerebral blood flow-pressure autoregulation curve during hypotension in normal rats. Anesthesiology 2002; 97:488–96
9. Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP: Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: Transcranial Doppler study in healthy volunteers. Br J Anaesth 2008; 100:240–4
10. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW: Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg 2012; 114:503–10
11. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, Koehler RC, Shaffner DH: Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. Stroke 2007; 38:2818–25
12. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, Pickard JD, Smielewski P: Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke 2010; 41:1963–8
13. Wong FY, Nakamura M, Alexiou T, Brodecky V, Walker AM: Tissue oxygenation index measured using spatially resolved spectroscopy correlates with changes in cerebral blood flow in newborn lambs. Intensive Care Med 2009; 35:1464–70
14. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, Brown C, Katz NM, Grams ME, Hogue CW: Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. Crit Care Med 2013; 41:464–71
15. 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

16. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr: Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41:1951–6
17. Zheng Y, Villamayor AJ, Merritt W, Pustavoitau A, Latif A, Bhambhani R, Frank S, Gurakar A, Singer A, Cameron A, Stevens RD, Hogue CW: Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. Neurocrit Care 2012; 17:77–84
18. Wagner BP, Pfenninger J: Dynamic cerebral autoregulatory response to blood pressure rise measured by near-infrared spectroscopy and intracranial pressure. Crit Care Med 2002; 30:2014–21
19. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW Jr: Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg 2014; 147:483–9
20. Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P, Czosnyka M, Hogue CW Jr: Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. Anesth Analg 2010; 110:321–8
21. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB: Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: Transcranial Doppler study under bispectral index monitoring. Br J Anaesth 2006; 97:333–9
22. Moerman A, Bové T, François K, Jacobs S, Deblaere I, Wouters P, De Hert S: The effect of blood pressure regulation during aortic coarctation repair on brain, kidney, and muscle oxygen saturation measured by near-infrared spectroscopy: A randomized, clinical trial. Anesth Analg 2013; 116:760–6
23. Stånge K, Lagerkranser M, Sollevi A: Nitroprusside-induced hypotension and cerebrovascular autoregulation in the anesthetized pig. Anesth Analg 1991; 73:745–52
24. Tzeng YC, MacRae BA, Ainslie PN, Chan GS: Fundamental relationships between blood pressure and cerebral blood flow in humans. J Appl Physiol (1985) 2014; 117:1037–48
25. Wagner BP, Ammann RA, Bachmann DC, Born S, Schibler A: Rapid assessment of cerebral autoregulation by near-infrared spectroscopy and a single dose of phenylephrine. Pediatr Res 2011; 69(5 pt 1):436–41
26. Sørensen H, Secher NH, Siebenmann C, Nielsen HB, Kohl-Bareis M, Lundby C, Rasmussen P: Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. Anesthesiology 2012; 117:263–70
27. Ogoh S, Sato K, Okazaki K, Miyamoto T, Secher F, Sørensen H, Rasmussen P, Secher NH: A decrease in spatially resolved near-infrared spectroscopy-determined frontal lobe tissue oxygenation by phenylephrine reflects reduced skin blood flow. Anesth Analg 2014; 118:823–9
28. Sørensen H, Rasmussen P, Sato K, Persson S, Olesen ND, Nielsen HB, Olsen NV, Ogoh S, Secher NH: External carotid artery flow maintains near infrared spectroscopy-determined frontal lobe oxygenation during ephedrine administration. Br J Anaesth 2014; 113:452–8
29. Sørensen H, Rasmussen P, Siebenmann C, Zaar M, Hvidtfeldt M, Ogoh S, Sato K, Kohl-Bareis M, Secher NH, Lundby C: Extra-cerebral oxygenation influence on near-infrared-spectroscopy-determined frontal lobe oxygenation in healthy volunteers: a comparison between INVOS-4100 and NIRO-200NX. Clin Physiol Funct Imaging 2015; 35:177–84
30. Davie SN, Grocott HP: Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116:834–40
31. Panerai RB: Cerebral autoregulation: From models to clinical applications. Cardiovasc Eng 2008; 8:42–59
32. Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, Walker AM: Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. Pediatrics 2008; 121:e604–11
33. Caicedo A, De Smet D, Naulaers G, Ameye L, Vanderhaegen J, Lemmers P, Van Bel F, Van Huffel S: Cerebral tissue oxygenation and regional oxygen saturation can be used to study cerebral autoregulation in prematurely born infants. Pediatr Res 2011; 69:548–53
34. Caicedo A, Naulaers G, Lemmers P, van Bel F, Wolf M, Van Huffel S: Detection of cerebral autoregulation by near-infrared spectroscopy in neonates: Performance analysis of measurement methods. J Biomed Opt 2012; 17:117003