

Near-infrared spectroscopy assessed cerebral oxygenation during open abdominal aortic aneurysm repair: relation to end-tidal CO₂ tension

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Abstract During open abdominal aortic aneurism (AAA) repair cerebral blood flow is challenged. Clamping of the aorta may lead to unintended hyperventilation as metabolism is reduced by perfusion of a smaller part of the body and reperfusion of the aorta releases vasodilatory substances including CO₂. We intend to adjust ventilation according end-tidal CO₂ tension (EtCO₂) and here evaluated to what extent that strategy maintains frontal lobe oxygenation (S_cO₂) as determined by near infrared spectroscopy. For 44 patients [5 women, aged 70 (48–83) years] S_cO₂, mean arterial pressure (MAP), EtCO₂, and ventilation were obtained retrospectively from the anesthetic charts. By clamping the aorta, S_cO₂ and EtCO₂ were kept stable by reducing ventilation (median, -0.8 l min^{-1} ; interquartile range, -1.1 to -0.4 ; $P < 0.001$). During reperfusion of the aorta a reduction in MAP by 8 mmHg (-15 to -1 ; $P < 0.001$) did not prevent an increase in S_cO₂ by 2 % (-1 to 4; $P < 0.001$) as EtCO₂ increased 0.5 kPa (0.1–1.0; $P < 0.001$) despite an increase in ventilation by 1.8 l min^{-1} (0.9–2.7; $P < 0.001$). Changes in S_cO₂ related to those in EtCO₂ ($r = 0.41$; $P = 0.0001$) and cerebral deoxygenation (-15 %) was noted in three patients while cerebral hyperoxygenation ($+15$ %) manifests in one patient. Thus changes in S_cO₂ were kept within acceptable limits (± 15 %) in 91 % of the patients. For the majority of the patients undergoing AAA repair S_cO₂ was kept within reasonable limits by reducing ventilation by approximately 1 l min^{-1} upon clamping of the aorta and

increasing ventilation by approximately 2 l min^{-1} when the lower body is reperfused.

Keywords Cerebral oximetry · Carbon dioxide · Near infrared spectroscopy · Vascular surgery · Ventilation

1 Introduction

Arterial carbon dioxide tension (P_aCO₂) is a potent moderator of cerebrovascular resistance by influence on its vascular smooth muscle tension [1], i.e. hypercapnia induces vasodilation and raises cerebral blood flow (CBF) while the reverse takes place during hypocapnia. CBF and P_aCO₂ are related linearly between 2 and 10 kPa while the CBF response becomes less steep outside that P_aCO₂ range [2]. The CBF response to changes in P_aCO₂, the so-called cerebrovascular CO₂ reactivity can be assessed by several methods, e.g. with near infrared spectroscopy (NIRS) determined cerebral oxygenation (S_cO₂), the brain's CO₂-reactivity is $2.1 \mu\text{mol L}^{-1} \text{ kPa}^{-1}$ oxygenated hemoglobin [3].

For perioperative evaluation NIRS is user-friendly for indirect assessment of changes in CBF but an influence from superficial tissue oxygenation has to be acknowledged [4]. Also it is important that NIRS detects the lower limit for cerebral autoregulation [5, 6] and thereby allows for interventions aimed to maintain S_cO₂ and thereby improve postoperative outcome [7–12]. The CO₂-reactivity, however, varies among patient groups, e.g. presenting with liver disease [13], atherosclerosis [14], or sepsis [15]. Moreover, with reperfusion of ischemic organs or limbs, hypercapnia is developed to an extent that it can become difficult to control CBF or S_cO₂ by adjusting ventilation and thereby P_aCO₂ [13, 16].

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For patients undergoing open abdominal aortic aneurysm repair, cross clamping of the aorta below the renal vessels reduces cardiac output (CO) and end-tidal CO₂ (EtCO₂) decreases if ventilation is not lowered to compensate for attenuated need of CO₂ elimination and, accordingly, S_cO₂ may become affected [17]. Conversely, with reperfusion of the lower body, vasodilatory substances including CO₂ are liberated to the circulation and provoke cerebral hyperperfusion as illustrated by a ~50 % increase in CBF [17, 18] that can lead to neurological complication and even death [19]. Following the observations by Liu et al. [17] the department intend to maintain S_cO₂ throughout open AAA repair by adjusting ventilation upon clamping and reperfusion of the aorta and this retrospective study evaluates, for forty-four patients, how well that ventilatory strategy is followed. Thus, we evaluated to what extent S_cO₂ was kept within reasonable limits (±15 %) and whether eventual changes in S_cO₂ during open AAA repair were related to those in EtCO₂ and thus ventilation.

2 Methods

Data were obtained from the anesthetic charts for patients undergoing open AAA repair (2010–2013). All patients in that period were considered eligibility with endovascular repair of the aneurysm as the only exclusion criterion. In total forty-four patients were enrolled for review that enables us to detect subtle changes ($<1 \pm 0.5$ %) in S_cO₂ (Table 1). Evaluation of data was initiated in accordance with guidelines provided by The National Committee on Health Research and following approval by the Local Ethical Committee (H-2-2012-114) and the Danish Data Protection Agency (2009-41-3617; 2012-41-1250). All patients gave informed consent to participate.

From the anesthetic charts we recorded heart rate (HR) and mean arterial pressure (MAP) obtained from a radial catheter in the arm with the highest non-invasively determined blood pressure before catheterizing the artery. The arterial wave form was exported from the blood pressure box to the Nexfin apparatus in which cardiac output (CO) was calculated by Modelflow[®] (Nexfin; BMEYE, Amsterdam, The Netherlands). Genders, age, height, weight of the patient were provided to the Nexfin prior to monitoring along with the anatomical site of the catheter. S_cO₂ (Invos 4100 Cerebral Oximeter, Somanetics, Troy, MI, USA) was recorded along with ventilation and EtCO₂ as a substitute for arterial CO₂. No threshold for either cerebral deoxygenation or hyperoxygenation exist for patients undergoing AAA repair, but significant cerebral deoxygenation was defined as a >15 % reduction in S_cO₂ relative to baseline

Table 1 Characteristics of patients

Age (years)	70 (48–83)
Co-morbidity (n)	
Hypertension	20
Arterial fibrillation	1
Ischemic heart disease	3
Diabetes	5
Chronic obstructive lung disease	6
Stroke	2
Duration of surgery (min)	165 (80–420)
Duration of aortic clamp (min)	70 (15–161)
Volume balance	
Blood loss (l)	2.2 (0.2–10.1)
Red packed cells (units)	5 (1–13)
Platelets (units)	2 (1–6)
Fresh frozen plasma (units)	4 (1–15)
Lactated ringer (l)	1.8 (0.7–3.2)
Colloids (l)	1.0 (0.2–1.5)
Mannitol (l)	0.3 (0.1–0.6)

Values are median (range)

[20] while a >15 % increase in S_cO₂ was considered to represent cerebral hyperoxygenation [21].

For postoperative pain treatment an epidural catheter (Th 8-9) was placed under cover of local anesthesia and a test dose of lidocaine (1 %; 4 ml) with adrenaline (5 mg ml⁻¹) was used to secure that the catheter was in place. A bolus dose of bupivacaine (3–5 ml, 0.5 %) was administered after induction of anesthesia followed by infusion of bupivacaine (4 ml h⁻¹). Anesthesia was induced by propofol (1–2 mg kg⁻¹) and fentanyl (1 µg kg⁻¹). Mask ventilation was established and cisatracurium (0.1–0.15 mg kg⁻¹) facilitated oral intubation and anesthesia maintained by propofol (0.08 mg kg⁻¹ min⁻¹) and remifentanyl (0.3–0.4 µg kg⁻¹ min⁻¹) (n = 32) or by sevoflurane (n = 12). Ephedrine (10 mg), calcium chloride (5 mmol L⁻¹) or phenylephrine (0.1 mg) was administered intravenously to raise blood pressure above 60 mmHg [22]. No vasodilatory agents were administered and in case of hypertension, administration of propofol, remifentanyl or sevoflurane could be considered to be increased. In general the choice of a particular anesthetic technique for lowering pressure is normally a decision made by the anesthesiologist but this did not appear to have occurred in the patients included for review. Blood products were administered to maintain hematocrit above 30 % (Table 1).

Variables were noted corresponding to three phases of the operation (dissection, aortic clamping and reperfusion) and changes evaluated by Friedman's repeated measures analysis of variance on ranks, followed by a Tukey–

Kramer post hoc test. If any differences between groups were detected we applied a Wilcoxon signed rank test. Differences between patients with or without inhalation of sevoflurane were evaluated using Kruskal–Wallis one way analysis of variance on ranks, followed by Dunn’s post hoc test. Correlations between variables were evaluated by the Spearman method and a *P* value <0.05 was considered statistical significant (SAS Institute Inc., Cary, NC, USA; Systat Software GmbH., Erkrath, Germany). Hemodynamic variables are presented as median change relative to baseline (interquartile range) while demographic data and perioperative administrations of vasopressors are presented as median (range).

3 Results

In Table 1 demographics, co-morbidity, duration of the surgery, and the perioperative blood loss are presented. Administration of ephedrine, calcium chloride and phenylephrine is listed in Table 2.

By clamping of the aorta ventilation was lowered (−0.8 l min^{−1}; −1.2 to −0.1; *P* < 0.001) to make EtCO₂ and thereby S_cO₂ stable. HR, MAP and CO did not change significantly (Fig. 1). Peak inspiratory pressure (16 cm H₂O; 16–17) and positive end-expiratory pressure (5 cm H₂O) were kept stable. Conversely, during reperfusion of the aorta S_cO₂ increased 2 % (−1 to 4; *P* < 0.001) as EtCO₂ became 0.5 kPa (0.1–1; *P* < 0.001) elevated although ventilation was increased by 1.8 l min^{−1} (0.9–2.7; *P* < 0.001) with an increase peak inspiratory pressure from 16 to 17 cm H₂O (*P* = 0.003). At the same time MAP decreased 8 mmHg (−15 to −1; *P* < 0.001) although CO increased 0.6 l min^{−1} (0.3–1.0; *P* < 0.001) while HR was stable.

Three patients experienced a >15 % reduction in S_cO₂ during aortic clamping although ventilation was reduced by 0.5–2.7 l min^{−1} that reduced EtCO₂ by 0.1–0.6 kPa. Conversely, one patient demonstrated a >15 % increase in S_cO₂ upon reperfusion of the aorta and for that patient ventilation was not increased. Thus, S_cO₂ was kept within

±15 % relative to baseline in 91 % of the patients (40 out of 44). Changes in S_cO₂ related to those in EtCO₂ (Spearman *r* = 0.41; *P* = 0.0001) (Fig. 2).

There were no differences in hemodynamic variables or ventilatory setting between patients who were exposed to intravenous or inhalation anesthesia. One of three patients who demonstrated a low S_cO₂ inhaled sevoflurane while the patient who demonstrated an increase in S_cO₂ was exposed to intravenous anesthesia.

4 Discussion

This retrospective cohort study on how well S_cO₂ is maintained by adjusting ventilation during open AAA repair finds that S_cO₂ was kept within an acceptable range in 91 % of the patients by reducing of ventilation by ~1 l min^{−1} during aortic clamping and increase it again by ~2 l min^{−1} upon reperfusion of the aorta. In support, S_cO₂ was related to EtCO₂ and in the patient who demonstrated a marked increase in S_cO₂ upon reperfusion of the lower body, ventilation was not increased. According to the anesthetic charts reviewed the present patients were exposed to less marked changes in cerebral oxygenation than those studied by Liu et al. [17] for whom no ventilatory adjustments were made.

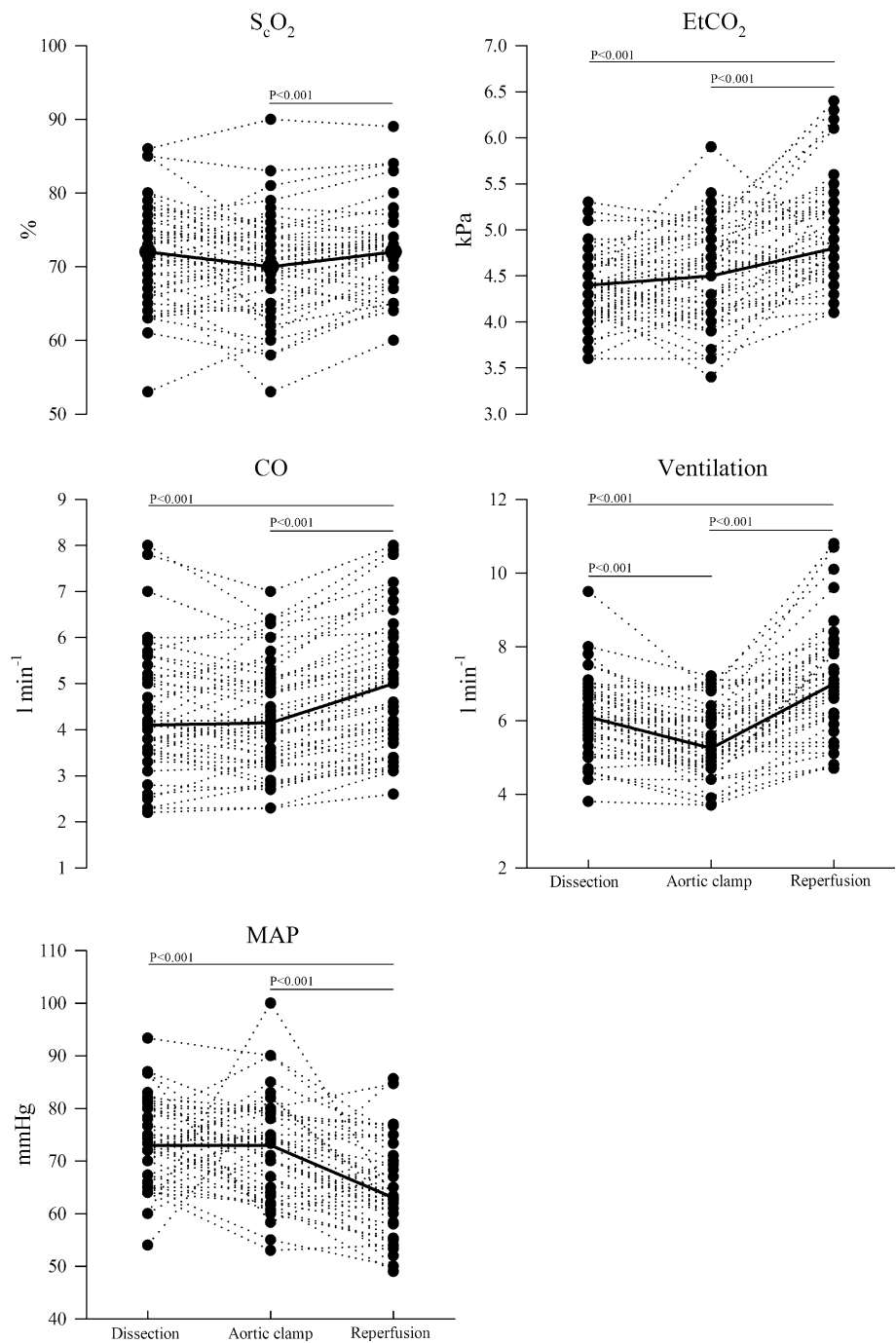
With clamping of the aorta below the renal arteries CO was stable although the lower part of the body is not or only marginally perfused. Thus, the need for CO₂ elimination is reduced and that affects CBF if ventilation is not reduced [17, 18]. Liu et al. [17] found that such unintended hyperventilation appears with a 13 % reduction in EtCO₂ and a consequent reduction in MCAV_{mean} by 12 % and in S_cO₂ by 4 % relative to the dissection phase. Although this reduction in S_cO₂ is small, some patients may demonstrate a significant reduction in S_cO₂, but for the twelve patients studied by Liu et al. [17] the individual values were not reported. In three of the present patients S_cO₂ was lowered to what we consider the threshold for cerebral deoxygenation [20] although ventilation was reduced by 0.5–2.7 l min^{−1}. Yet for two of these patients there was a reduction

Table 2 Administration of vasopressors

	Ephedrine	Calcium chloride	Phenylephrine
Dissection	20 (10–50) (n = 43)	20 (2.5–20) (n = 3)	0.2 (0.1–0.6) (n = 10)
Dissection (last 15 min)	10 (5–15) (n = 14)	5 (n = 1)	0.1 (0.1–0.1) (n = 3)
Aortic clamp	10 (5–30) (n = 15)	7.5 (2.5–25) (n = 26)	0.1 (0.1–0.3) (n = 11)
Aortic clamp (first 15 min)	10 (5–20) (n = 8)	5 (2.5–10) (n = 14)	0.1 (n = 1)
Reperfusion	10 (5–40) (n = 24)	5 (2.5–20) (n = 24)	0.1 (0.05–1.1) (n = 24)
Reperfusion (first 15 min)	10 (5–20) (n = 13)	5 (2.5–10) (n = 17)	0.1 (0.05–0.4) (n = 15)

Dosages of ephedrine (mg), calcium chloride (mmol) and phenylephrine (mg). Median (range) and the number of patients. Number of patients, 44

Fig. 1 Individual changes in near infrared spectroscopy determined cerebral oxygenation (S_cO_2), cardiac output (CO), minute ventilation, mean arterial pressure (MAP), and end-tidal CO_2 ($EtCO_2$), during dissection, aortic clamping, and reperfusion of the aorta during open aortic aneurism repair ($n = 44$). *Solid line* indicates median



in $EtCO_2$ by ~ 0.5 kPa and therefore the reduction in ventilation has been inadequate.

Reperfusion of the aorta liberates CO_2 , lactate and other vasodilatory substances such as prostacyclin to the circulation [23] and $EtCO_2$ increases, e.g. by 44 % after reperfusion of the aorta if ventilation is not adjusted [17]. We report one event of cerebral hyperoxygenation and in that patient no ventilatory adjustments were made. Also inadequate ventilatory adjustment is likely to explain the

cerebral hyperperfusion demonstrated by an increase by 45–53 % (in some patients by 104 %) in $MCAv_{mean}$ within 20 min after reperfusion of the aorta [17, 18]. Liu et al. [17] identified a relative increase in S_cO_2 by 9 % upon reperfusion while the increase was only by 3 % in this study where ventilation was adjusted to aim for at stable $EtCO_2$.

Cerebrovascular disease contributes to death after elective AAA repair (7 %) and is even more significant in

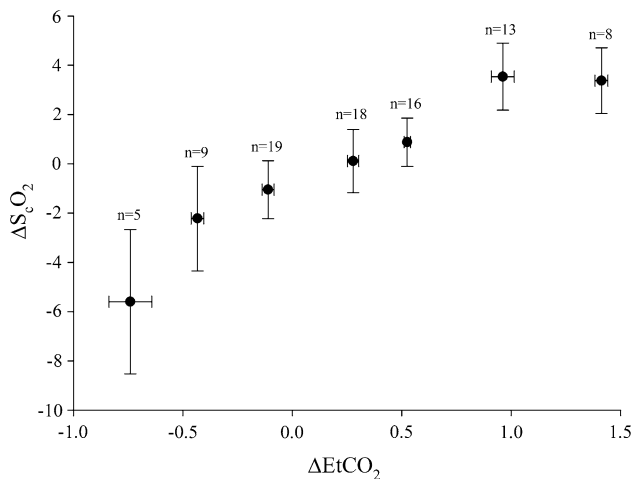


Fig. 2 Near infrared spectroscopy determined cerebral oxygenation (S_cO_2) and end-tidal CO_2 tension ($EtCO_2$) during open abdominal aorta aneurysm (AAA) repair (% changes from baseline; \pm SEM) (Spearman $r = 0.4$; $P = 0.0001$; $n = 88$). Number of patients indicated

patients presenting with a ruptured aneurysm (13 %) [24]. However, for the early postoperative period after AAA repair neurological outcome is not evaluated in regard to changes in CBF and in turn S_cO_2 . In patients undergoing carotid endarterectomy, symptoms of cerebral hyperperfusion including headache, vomiting, confusion, seizures, and hemorrhage are reported with an increase in $MCAV_{mean}$ by 100–300 % or a >15 % increase in S_cO_2 [21, 25, 26]. A cerebral hyperperfusion syndrome can manifest immediately or up to 30 days after carotid endarterectomy and if left untreated mortality is high [26]. We do not expect patients undergoing AAA repair to develop a cerebral hyperperfusion syndrome as the increase in S_cO_2 after open AAA repair lasts typically less than half an hour. However, even brief episodes of hyperoxygenation may affect Starling forces within the cerebral capillaries and result in endothelial damage. In general, adequate oxygen delivery to the brain during anesthesia secures rapid recovery as exemplified after thoracic aortic repair [10] as for patients undergoing cardiothoracic [7–10, 27], orthopedic [11], or major abdominal surgery [12]. Accordingly, also patients undergoing AAA surgery may benefit if S_cO_2 is maintained stable.

The danger of a high cerebral perfusion is illustrated in patients with end-stage liver disease [13, 19]. During reperfusion of the grafted liver patients are subjected to cerebral hyperperfusion that may persist into the postoperative period and lead to brain death [19]. Despite adjustment of ventilation during liver transplantation surgery, it remains difficult to keep S_cO_2 stable [16] as S_cO_2 seems to increase more in liver compared AAA repair patients for a given change in $EtCO_2$. Thus, for patients

with liver disease other vasodilating substances than CO_2 may affect the cerebral vasculature [28, 29]. As determined by ^{133}Xe clearance CBF demonstrates an increase by 20 % with reperfusion of the liver [13] and the increase in P_aCO_2 may mitigate the CO_2 -reactivity because of near-maximal cerebral vasodilatation, i.e. the linear relationship between CBF and P_aCO_2 becomes less steep with high P_aCO_2 values [2]. As demonstrated for the AAA patients, control of ventilations can secure $EtCO_2$ and thereby S_cO_2 because these patients, in contrast to those with liver disease, demonstrates a CO_2 reactivity similar to healthy subjects [3] (Fig. 2).

In the reported patients, ephedrine was preferred by the anesthesiologist in the dissection phase whereas calcium chloride was administered typically during aortic clamping (Table 2). CO has been reported to decrease by 2.5 l min^{-1} with a slight increase in MAP (by 6 mmHg) upon aortic clamping [17], however, in the present study the administration of ephedrine and calcium chloride may have prevented such a reduction in CO [22]. The use of vasopressors was balanced during reperfusion of the aorta. Phenylephrine reduces S_cO_2 by vasoconstriction within extra-cerebral tissue [4, 30] that may have caused false positive events of cerebral deoxygenation, but none of the three patient with cerebral deoxygenation received phenylephrine. As phenylephrine is administered frequently during reperfusion, we cannot exclude that S_cO_2 , as an expression of CBF, may be an underestimate due to skin vasoconstriction. However, we bear in mind that the impact of phenylephrine on S_cO_2 seems to depend on preload to the heart [31] and skin blood flow may already be near-maximal comprised by release of catecholamines with reduction of the central blood volume [32].

Limitations of this retrospective observational study are to be mentioned. Hemorrhage amounted to 2.2 l in the presented cohort of patients that along with fluid loss may compromise organ perfusion, however, as blood products were continuously administered to secure hematocrit >30 % we find that unlikely. Twelve patients inhaled sevoflurane, which, in contrast to other inhalation anesthetics, does not have a dose related depressive effect on the cerebral autoregulation [33]. Combination of propofol and remifentanyl anesthesia preserves cerebral autoregulation and in the studied population no differences between hemodynamic variables among the two groups were observed. Also hypotension develops in up to 95 % of AAA patients in response to a so-called mesenteric traction syndrome [34] and both manifestations could affect CBF and in turn S_cO_2 . The duration of S_cO_2 below the considered threshold (>15 %) was not noted. Although no data are available for patients undergoing AAA repair, it seems that the area under the threshold correlates to outcome during surgical aortic arch repair [10]. $EtCO_2$ is a trend

monitor for continuously assessment of $P_a\text{CO}_2$ and EtCO_2 is typically 0.5 kPa lower than $P_a\text{CO}_2$, but we acknowledge that this ratio differs with changes in pulmonary circulation, volume of dead space, and ventilatory strategy applied during anesthesia [35, 36]. Diminished cerebrovascular CO_2 reactivity may result in a linear relationship between $S_c\text{O}_2$ and MAP, however, the individual CO_2 reactivity was not assessed before surgical incision. Also this study did not address eventual postoperative cerebral complication in relation to deviations in $S_c\text{O}_2$ and for that purpose a larger population of patients is in need.

In summary, this retrospective observational study finds that cerebral hyperoxygenation during reperfusion of the aorta during open AAA repair is dominated by an increase in EtCO_2 as an indication of $P_a\text{CO}_2$. With a $\sim 1 \text{ l min}^{-1}$ decrease and a $\sim 2 \text{ l min}^{-1}$ increase in ventilation during clamping and reperfusion of the aorta, respectively, cerebral oxygenation was kept within $\pm 15 \%$ relative to baseline, which is a similar deviation going from, e.g. a supine to standing position [37]. Yet for some patients control of EtCO_2 was inaccurate, and we can only speculate whether significant deviations in $S_c\text{O}_2$ affects outcome after open AAA repair.

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Conflict of interest The authors declared no conflict of interest.

References

- Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol Scand*. 1983;117(2):203–11.
- 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 Psychiatry*. 1965;28(5):449–52.
- Smielewski P, Kirkpatrick P, Minhas P, Pickard JD, Czosnyka M. Can cerebrovascular reactivity be measured with near-infrared spectroscopy? *Stroke*. 1995;26(12):2285–92.
- 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(2):263–70.
- 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(3):503–10.
- Nissen P, Pacino H, Frederiksen HJ, Novovic S, Secher NH. Near-infrared spectroscopy for evaluation of cerebral autoregulation during orthotopic liver transplantation. *Neurocrit Care*. 2009;11(2):235–41.
- Colak Z, Borojevic M, Bogovic A, Ivancan V, Biocina B, Majeric-Kogler V. Influence of intraoperative cerebral oximetry monitoring on neurocognitive function after coronary artery bypass surgery: a randomized, prospective study. *Eur J Cardiothorac Surg*. 2015;47(3):447–54.
- Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM 3rd, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thorac Surg*. 2009;87(1):36–44.
- Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg*. 2007;104(1):51–8.
- Fischer GW, Lin HM, Krol M, Galati MF, Di Luozzo G, Griep RB, Reich DL. Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. *J Thorac Cardiovasc Surg*. 2011;141(3):815–21.
- Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, Lowery D, Corbett A, Wesnes K, Katsaiti E, Arden J, Amoako D, Prophet N, Purushothaman B, Green D. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. *PLoS ONE*. 2012;7(6):e37410.
- Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, Fierro G, De Cosmo G, Servillo G. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg*. 2005;101(3):740–7.
- Larsen FS, Ejlersen E, Strauss G, Rasmussen A, Kirkegaard P, Hansen BA, Secher N. Cerebrovascular metabolic autoregulation is impaired during liver transplantation. *Transplantation*. 1999;68(10):1472–6.
- Kawata R, Nakakimura K, Matsumoto M, Kawai K, Kunihiro M, Sakabe T. Cerebrovascular CO_2 reactivity during anesthesia in patients with diabetes mellitus and peripheral vascular disease. *Anesthesiology*. 1998;89(4):887–93.
- Terborg C, Schummer W, Albrecht M, Reinhart K, Weiller C, Rother J. Dysfunction of vasomotor reactivity in severe sepsis and septic shock. *Intensive Care Med*. 2001;27(7):1231–4.
- Sørensen H, Grocott HP, Niemann M, Rasmussen A, Hillingsø JG, Frederiksen HJ, Secher NH. Ventilatory strategy during liver transplantation: implications for near-infrared spectroscopy-determined frontal lobe oxygenation. *Front Physiol*. 2014;5:321.
- Liu G, Burcev I, Pott F, Ide K, Horn A, Secher NH. Middle cerebral artery flow velocity and cerebral oxygenation during abdominal aortic surgery. *Anaesth Intensive Care*. 1999;27(2):148–53.
- Pittella G, Benanti CF, Palombo C, Kozakova M, Distante A, Giunta F. Evaluation of cerebral perfusion during aortic clamping and cross-clamping in patients undergoing resection for abdominal aortic aneurysm. A study with transcranial doppler. *Minerva Anestesiol*. 1997;63(3):69–75.
- Larsen FS, Pott F, Hansen BA, Ejlersen E, Knudsen GM, Clemmesen JD, Secher NH. Transcranial doppler sonography may predict brain death in patients with fulminant hepatic failure. *Transpl Proc*. 1995;27(6):3510–1.
- Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke*. 2006;37(11):2720–5.
- Pennekamp CWA, Immink RV, Den Ruijter HM, Kappelle LJ, Ferrier CM, Bots ML, Buhre WF, Moll FL, De Borst GJ. Near-infrared spectroscopy can predict the onset of cerebral hyperperfusion syndrome after carotid endarterectomy. *Cerebrovasc Dis*. 2012;34(4):314–21.
- Kitchen CC, Nissen P, Secher NH, Nielsen HB. Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension. *Front Physiol*. 2014;5:407.

23. Kretzschmar M, Klein U, Palutke M, Schirrmeyer W. Reduction of ischemia-reperfusion syndrome after abdominal aortic aneurysmectomy by N-acetylcysteine but not mannitol. *Acta Anaesthesiol Scand*. 1996;40(6):657–64.
24. Cho JS, Glowiczki P, Martelli E, Harmsen WS, Landis ME, Cherry KJ Jr, Bower TC, Hallett JW Jr. Long-term survival and late complications after repair of ruptured abdominal aortic aneurysms. *J Vasc Surg*. 1998;27(5):813–9.
25. Jørgensen LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. *Eur J Vasc Surg*. 1993;7(4):370–9.
26. van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, de Leeuw PW. Cerebral hyperperfusion syndrome. *Lancet Neurol*. 2005;4(12):877–88.
27. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum*. 2004;7(5):376–81.
28. Philips BJ, Armstrong IR, Pollock A, Lee A. Cerebral blood flow and metabolism in patients with chronic liver disease undergoing orthotopic liver transplantation. *Hepatology*. 1998;27(2):369–76.
29. Roth E, Steininger R, Winkler S, Langle F, Grunberger T, Fugger R, Muhlbacher F. L-Arginine deficiency after liver transplantation as an effect of arginase efflux from the graft. Influence on nitric oxide metabolism. *Transplantation*. 1994;57(5):665–9.
30. Sørensen H, Rasmussen P, Sato K, Persson S, Olesen ND, Nielsen HB, Olsen NV, Ogoh S, Secher NH. External carotid artery flow maintains NIRS-determined frontal lobe oxygenation during ephedrine administration. *Br J Anaesth*. 2014;113(3):452–8.
31. Cannesson M, Jian Z, Chen G, Vu TQ, Hatib F. Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank–Starling relationship. *J Appl Physiol*. 2012;113(2):281–9.
32. Sander-Jensen K, Secher NH, Astrup A, Christensen NJ, Giese J, Schwartz TW, Warberg J, Bie P. Hypotension induced by passive head-up tilt: endocrine and circulatory mechanisms. *Am J Physiol*. 1986;251(4 Pt 2):R742–8.
33. Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *Br J Anaesth*. 1997;79(4):469–72.
34. Seltzer JL, Ritter DE, Starsnic MA, Marr AT. The hemodynamic response to traction on the abdominal mesentery. *Anesthesiology*. 1985;63(1):96–9.
35. Fletcher R, Jonson B. Dead-space and the single breath test for carbon dioxide during anaesthesia and artificial ventilation. Effects of tidal volume and frequency of respiration. *Br J Anaesth*. 1984;56(2):109–19.
36. Askrog V. Changes in (a-A)CO₂ difference and pulmonary artery pressure in anesthetized man. *J Appl Physiol*. 1966;21(4):1299–305.
37. Immink RV, Secher NH, Roos CM, Pott F, Madsen PL, van Lieshout JJ. The postural reduction in middle cerebral artery blood velocity is not explained by PaCO₂. *Eur J Appl Physiol*. 2006;96(5):609–14.