Preserved frontal lobe oxygenation following calcium chloride for treatment of anesthesia-induced hypotension

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Vasopressor agents may affect cerebral oxygenation \( (rScO_2) \) as determined by near-infrared spectroscopy on the forehead. This case series evaluated the effect of calcium chloride vs. \( \alpha \) and \( \beta \)-adrenergic receptor agonists on \( rScO_2 \) in patients \( (n = 47) \) undergoing surgery during i.v. anesthesia. Mean arterial pressure (MAP) and cardiac output (CO) were assessed by Model-flow® and ephedrine \( (55 \pm 3 \text{ vs. } 74 \pm 9\text{ mmHg}; \ 10 \text{ mg}, n = 9) \), phenylephrine \( (51 \pm 5 \text{ vs. } 78 \pm 9\text{ mmHg}; \ 0.1 \text{ mg}, n = 11) \), adrenaline \( (53 \pm 3 \text{ vs. } 72 \pm 11\text{ mmHg}; \ 1\text{–}2 \text{\&mu}g, n = 6) \), noradrenaline \( (53 \pm 5 \text{ vs. } 72 \pm 12\text{ mmHg}; \ 2\text{–}4 \text{\&mu}g, n = 11) \), and calcium chloride \( (49 \pm 7 \text{ vs. } 57 \pm 16\text{ mmHg}; \ 5\text{ mmol}, n = 10) \) increased MAP (all \( P < 0.05 \)). CO increased with ephedrine \( (4.3 \pm 0.9 \text{ vs. } 5.3 \pm 1.2, P < 0.05) \) and adrenaline \( (4.7 \pm 1.2 \text{ vs. } 5.9 \pm 1.1 \text{ l/min}; P = 0.07) \) but was not significantly affected by phenylephrine \( (3.9 \pm 0.7 \text{ vs. } 3.6 \pm 1.0\text{ l/min}), \) noradrenaline \( (3.8 \pm 1.2 \text{ vs. } 3.7 \pm 0.7\text{ l/min}), \) or calcium chloride \( (4.0 \pm 1.4 \text{ vs. } 4.1 \pm 1.5\text{ l/min}), \) Following administration of \( \beta \)-adrenergic agents and calcium chloride \( rScO_2 \) was preserved while after administration of \( \alpha \)-adrenergic drugs \( rScO_2 \) was reduced by app. 2% \( (P < 0.05) \). Following \( \alpha \)-adrenergic drugs to treat anesthesia-induced hypotension tissue oxygenation is reduced while the use of \( \beta \)-adrenergic agonists and calcium chloride preserve tissue oxygenation.

Keywords: brain, blood pressure, cardiac output, NIRS, cerebral oxygenation, cerebral oximetry

INTRODUCTION

Cerebral autoregulation has a lower limit (Paulson et al., 1990) and following induction of anesthesia blood pressure may decrease to what is considered to be below that level. Accordingly, patients receive intravenous administration of vasopressor agents such as phenylephrine (an \( \alpha \)-adrenergic receptor agonist) or ephedrine that stimulates both \( \alpha \) and \( \beta \)-adrenergic receptors. Bolus calcium chloride could also increase blood pressure (Ellender and Skinner, 2008) by an increase in intracellular calcium to increase cardiac stroke volume via an effect on myocytes and vascular resistance via increased contraction of smooth muscles. Also calcium chloride may increase venous return by unloading the splanchnic reservoir. Thus, with administration of calcium chloride cardiac output \( (CO) \) increases without affecting heart rate \( (HR) \) (Ellender and Skinner, 2008) contrasting ephedrine that has the potential to increase both HR and CO.

Phenylephrine decreases the near infrared spectroscopy \( (\text{NIRS}) \) determined frontal lobe oxygenation \( (rScO_2) \) (Brassard et al., 2010, 2014; Nissen et al., 2010; Meng et al., 2011; Foss et al., 2014) related to vasoconstriction in extracranial vasculature rather than to a decrease in cerebral oxygenation (Ogoh et al., 2011, 2014; Sorensen et al., 2012). In this study patients undergoing major abdominal surgery were recruited to evaluate \( rScO_2 \) following routine administration of vasoactive drugs to treat a drop in blood pressure by induction of anesthesia. We used bolus calcium chloride along with the vasopressor agents phenylephrine, ephedrine, adrenaline or noradrenaline depending on the choice of the anesthesiologist. We tested the hypothesis that administration of ephedrine, adrenaline and calcium chloride to treat anesthesia-induced hypotension would preserve \( rScO_2 \) while \( rScO_2 \) would be reduced following administration of drugs that stimulate \( \alpha \)-adrenergic receptors (phenylephrine and noradrenaline).

METHODS

In a pilot-like prospective study-design as approved by the regional ethical committee (H-1-2009-107) we included predominantly patients planned for major abdominal surgery. In 47 patients \( (\text{age } 63 \pm 7\text{ years}, \text{ height } 176 \pm 7\text{ cm}, \text{ weight } 78 \pm 16\text{ kg}; 28\text{ males; mean } \pm 1SD) \) this selection of cases tested the effect of different vasopressor agents on anesthesia-induced hypotension and \( rScO_2 \). Most patients were admitted for planned surgery including the liver, pancreas, esophagus, ventricle, or colon. In one case the spleen was the target for surgery and an other patient suffered from a retroperitoneal tumor. Three patients underwent vascular surgery and one patient was in surgery for hydronephrosis. Diabetes requiring insulin and the use of anti-hypertensive medication were considered to contradict inclusion in the evaluated series of patients. An increase in bilirubin was also an exclusion criterion due to the influence of bilirubin on near-infrared light absorption (Madsen et al., 2000).

The patients were exposed to at least 6 h of fast and orally intake of clear fluids was stopped 2 h before surgery. Three-lead electrocardiography monitored HR and pulse oximetry assessed arterial hemoglobin \( O_2 \text{ saturation} \ (\text{SpO}_2) \). A hand vein was used for administration of fluid and anesthetics. According to

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local guidelines, a radial artery catheter (20 gage; 1.1 mm) was, after local anesthesia, inserted in the arm with the highest non-invasively determined systolic blood pressure and the catheter was kept patent by isotonic saline (3 ml/h) through to a transducer (Edwards Life Sciences, Irvine, CA, USA) positioned at the level of the heart. For surgery an epidural catheter was placed at Th. 8–10 in the lateral decubitus position and under local anesthesia, lidocaine (3 ml, 10 mg/ml) with adrenaline (5 μg/ml) was administered to test for intravascular or intrathecal placement.

A two channel cerebral oximeter (INVOS 5100C, Somanetics, Troy, MI, USA) detected rScO2 that represents hemoglobin oxygen saturation in the tissue beneath the sensor as the ratio between oxygenated and total hemoglobin. As approved by the US Food and Drug Administration (510k-080769), the INVOS 5100C-determined rScO2 is considered a trend monitor of the hemoglobin O2 saturation for skin, scalp, and cortical tissue. With the NIRS-probe applied on the forehead it is assumed that capillaries within the frontal lobe contribute to light absorbance (Madsen and Secher, 1999) but skin, subcutaneous tissue and the scalp blood flow also influences the INVOS-determined rScO2 (Davie and Grocott, 2012). rScO2 was determined at least 2 cm above the eyebrows to limit an influence from the frontal sinus on rScO2 (Tubbs et al., 2002). Cardiovascular variables including mean arterial pressure (MAP), HR, cardiac stroke volume (SV) and thus CO were assessed invasively by Model-flow® (Nexfin, Troy, MI, USA) detected rScO2 that represents hemoglobin oxygen saturation in the tissue beneath the sensor as the ratio between oxygenated and total hemoglobin. As approved by the US Food and Drug Administration (510k-080769), the INVOS 5100C-determined rScO2 is considered a trend monitor of the hemoglobin O2 saturation for skin, scalp, and cortical tissue. With the NIRS-probe applied on the forehead it is assumed that capillaries within the frontal lobe contribute to light absorbance (Madsen and Secher, 1999) but skin, subcutaneous tissue and the scalp blood flow also influences the INVOS-determined rScO2 (Davie and Grocott, 2012). rScO2 was determined at least 2 cm above the eyebrows to limit an influence from the frontal sinus on rScO2 (Tubbs et al., 2002). Cardiovascular variables including mean arterial pressure (MAP), HR, cardiac stroke volume (SV) and thus CO were assessed invasively by Model-flow® (Nexfin, B.V, Amsterdam, The Netherlands; Bogert and van Lieshout, 2005).

Anesthesia was induced with propofol (2 mg/kg) and maintained with propofol (0.08 mg/kg/min) and remifentanil (0.3–0.4 μg/kg/min). For ventilation a Dräger CATO (M32040, Lübeck, Germany) in volume-controlled mode was adjusted to an end-tidal CO2 tension of 4–4.5 kPa and a positive end-expiratory pressure of 5 cm H2O was used. When the patient was orally intubated, the inspiratory O2 fraction was set to 0.7 to preclude rScO2 (Tubbs et al., 2002). Cardiovascular variables including mean arterial pressure (MAP), HR, cardiac stroke volume (SV) and thus CO were assessed invasively by Model-flow® (Nexfin, B.V, Amsterdam, The Netherlands; Bogert and van Lieshout, 2005).

Bolus calcium chloride maintained HR, SV, and CO and, as intended MAP increased (from 49 ± 7 to 57 ± 16 mmHg, P < 0.05) (Table 2, Figure 1). The other vasoactive agents also influenced cardiovascular variables: following administration of adrenaline SV tended to increase (P = 0.08) and as HR was maintained (P = 0.71) also CO tended to increase (by 25%, P = 0.07). Similarly, administration of ephedrine increased CO (P < 0.05) due to a non-significant change in HR (P = 0.26) and SV (P = 0.10). Both adrenaline and ephedrine increased MAP by 19 mmHg. Phentylephrine and noradrenaline maintained HR, SV, and CO with an increase in MAP by 27 and 20 mmHg, respectively.

The effect of vasoactive therapy on the NIRS determined rScO2 are shown in Table 2 and Figure 1. In patients treated with adrenaline and ephedrine rScO2 was not affected significantly and when these data were pooled into one group of patients treated with β-adrenergic drugs, rScO2 remained statistically unaffected: there was an increase in rScO2 for five patients and for seven patients rScO2 decreased without relation to changes in MAP or CO. After noradrenaline and phentylephrine a small but non-significant reduction in rScO2 was noted for each vasoactive agent. However, with data evaluated as one group (α-adrenergic receptor agonists; noradrenaline and phentylephrine), seven patients with noradrenaline and seven patients with phentylephrine demonstrated lowered rScO2 after drug administration while for only six patients rScO2 increased (Figure 2). For two of these patients rScO2 decreased almost 10%.

### Table 1 | Patient characteristics in five groups of patients who received vasoactive therapy to treat anesthesia-induced hypotension.

| Variable       | Ephedrine (n = 9) | Adrenaline (n = 6) | Phentylephrine (n = 11) | Noradrenaline (n = 11) | Calcium chloride (n = 10) |
|----------------|------------------|-------------------|------------------------|-----------------------|--------------------------|
| Age (yrs)      | 67 ± 3           | 56 ± 11*          | 64 ± 7                 | 64 ± 3                | 60 ± 9                   |
| Weight (kg)    | 84 ± 18          | 76 ± 13           | 76 ± 9                 | 76 ± 16               | 80 ± 22                  |
| Height (cm)    | 178 ± 5          | 174 ± 6           | 179 ± 7                | 177 ± 7               | 172 ± 7                  |

Variable are mean ± SD. *Difference between Ephedrine and Adrenaline; P < 0.05.
while CO increased (0.5 and 2.3 L/min) and for the whole group of patients (α-adrenergic receptor agonists) rScO2 decreased 2%. After calcium chloride in four patients rScO2 decreased (1–5%) and while rScO2 was unchanged (n = 2) or increased (up to 6%) in the other eight patients, rScO2 was not statistically affected by calcium chloride. Correlations between rScO2 and MAP or CO were not observed.

**DISCUSSION**

This case series of 47 patients confirms that following anesthesia-induced hypotension in elective surgical patients, a vasopressor agent including calcium chloride increases MAP. The new finding is that frontal lobe oxygenation (rScO2,) as determined by near-infrared spectroscopy was not significantly affected following the use of calcium chloride for treatment of anesthesia-induced hypotension. A similar finding was observed with the use of ephedrine, phenylephrine, adrenaline, and noradrenaline as rScO2 remained at levels similar to those established before drug administration. However, when data from patients treated with α-adrenergic receptor agonists (phenylephrine and noradrenaline) were pooled into one group and patients treated with β-adrenergic drugs (adrenaline or ephedrine) were sampled in an other group, rScO2 decreased 2% after α-adrenergic drug administration but remained unaffected with administration of β-adrenergic stimulating drugs. This observation supports results obtained in patients (Nisen et al., 2010; Meng et al., 2011; Brassard et al., 2014) and healthy awake subjects (Brassard et al., 2010). Although a 2% reduction in rScO2 seems small, the change is in the magnitude as induced by hyperventilation that lowers arterial CO2 partial pressure with development of presyncope symptoms (Madsen and Secher, 1999). Also Thomas et al. (2009) report ~6% drop in cerebral oxygenation at presyncope.

Why rScO2 is reduced after α-adrenergic drugs and not after administration of β-adrenergic-therapy and calcium chloride...
remains unclear. In patients with intact cerebral autoregulation, the decrease in rScO$_2$ after phenylephrine and noradrenaline administration is associated with concordant reduction in CO, whereas rScO$_2$ remains unchanged when CO was maintained with ephedrine (Meng et al., 2011). This observation supports that changes in CO, independently of arterial pressure, affect cerebral hemodynamics (Ogoh et al., 2005). Cerebral arteries are abundantly innervated by sympathetic fibers (Sandor, 1999) and the decrease in rScO$_2$ after administration of α-adrenergic drugs could be by direct α-receptor-mediated cerebral vasoconstriction. An influence of cutaneous vasoconstriction beneath the NIRS optode, however, has to be considered (Davie and Grocott, 2012; Sørensen et al., 2012).

The increase in MAP by vasoactive therapy was expected and the use of bolus calcium chloride also increased MAP even in patients without a suspected reduction in plasma ionized calcium. Indication for the use of calcium chloride is more clear after the use of blood products containing citrate that may lead to hypocalcemia (Jawan et al., 2003) and hemodynamic instability (Marquez et al., 1986). Thus, calcium chloride restores the levels of ionized calcium in blood and in turn also MAP. Despite the effect of vasoactive agents on MAP was similar with the use of different drugs, the rise in pressure was achieved differently. Both ephedrine and adrenaline increased CO but noradrenaline. When data from patients treated with noradrenaline and phenylephrine were pooled into one group, CO was restored in patients without a suspected reduction in plasma ionized calcium chloride for treatment of anesthesia-induced hypotension is substantiated.

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