External carotid artery flow maintains near infrared spectroscopy-determined frontal lobe oxygenation during ephedrine administration

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Background. Phenylephrine and ephedrine affect frontal lobe oxygenation (S\textsubscript{O\textsubscript{2}}) differently when assessed by spatially resolved near infrared spectroscopy. We evaluated the effect of phenylephrine and ephedrine on extra- vs intra-cerebral blood flow and on S\textsubscript{O\textsubscript{2}}.

Methods. In 10 healthy males (age 20–54 yr), phenylephrine or ephedrine was infused for an ∼20 mm Hg increase in mean arterial pressure. Cerebral oxygenation (S\textsubscript{O\textsubscript{2}}) was calculated from the arterial and jugular bulb oxygen saturations. Blood flow in the internal carotid artery (ICAf) and blood flow in the external carotid artery (ECAf) were assessed by duplex ultrasonography. Invas-5100c (S\textsubscript{invos\textsubscript{O\textsubscript{2}}}) and Foresight (S\textsubscript{fore\textsubscript{O\textsubscript{2}}}) determined S\textsubscript{O\textsubscript{2}} while forehead skin oxygenation (S\textsubscript{skin\textsubscript{O\textsubscript{2}}}) was assessed.

Results. Phenylephrine reduced S\textsubscript{invos\textsubscript{O\textsubscript{2}}} by 6.9% (95% confidence interval: 4.8–9.0%; P<0.0001), S\textsubscript{invos\textsubscript{O\textsubscript{2}}} by 10.5 (8.2–12.9%; P<0.0001), and ECAf (6–28%; P=0.0001), but increased ICAf (5–21%; P=0.003) albeit with no consequence for S\textsubscript{skin\textsubscript{O\textsubscript{2}}} or S\textsubscript{av\textsubscript{O\textsubscript{2}}}. In contrast, S\textsubscript{fore\textsubscript{O\textsubscript{2}}} was maintained with administration of ephedrine while S\textsubscript{invos\textsubscript{O\textsubscript{2}}} and S\textsubscript{av\textsubscript{O\textsubscript{2}}} decreased [by 3.1 (0.7–4.5%; P=0.017) and 2.1 (0.5–3.3%; P=0.012)] as arterial carbon dioxide pressure decreased (P=0.003). ICAf was stable and ECAf increased by 11 (4–18%; P=0.005) with administration of ephedrine while S\textsubscript{skin\textsubscript{O\textsubscript{2}}} did not change.

Conclusions. The effect of phenylephrine on S\textsubscript{O\textsubscript{2}} is governed by a decrease in external carotid blood flow since it increases cerebral blood flow as determined by flow in the internal carotid artery. In contrast, S\textsubscript{O\textsubscript{2}} is largely maintained with administration of ephedrine because blood flow to extracerebral tissue increases.

Keywords: cerebral blood flow; cerebral oxygenation; ephedrine; phenylephrine; skin blood flow

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Anaesthesia impedes sympathetic control of vascular tone and regulation of arterial pressure,1 possibly to an extent that perfusion of the brain is affected. To prevent episodes where cerebral blood flow (CBF) and oxygenation are compromised, vasopressor agents including ephedrine, phenylephrine, and norepinephrine are administered to maintain arterial pressure within what is considered to represent the cerebral autoregulatory range.2 Frontal lobe oxygenation (S\textsubscript{O\textsubscript{2}}) can be monitored by near infrared spectroscopy (NIRS), and S\textsubscript{O\textsubscript{2}} identifies the lower limit of cerebral autoregulation1 and can be used to guide so-called individualized goal-directed fluid therapy.6 Perioperative optimization of S\textsubscript{O\textsubscript{2}} carries the potential to improve postoperative outcomes in cardiac5 6 and elderly patients,7 while a low preoperative S\textsubscript{O\textsubscript{2}} might predict adverse postoperative outcomes.8 S\textsubscript{O\textsubscript{2}} is validated by correlation to a calculation of cerebral tissue oxygenation based on the arterial to internal jugular venous oxygen difference and taking changes in CBF into account.9 Spatially resolved NIRS (SR-NIRS) intends to provide an absolute value for cerebral oxygenation and attenuates the superficial tissue contribution to S\textsubscript{O\textsubscript{2}} by emphasizing light returning from ‘deep’ tissues.10

In both awake and anaesthetized humans, an influence of extracranial tissue oxygenation on S\textsubscript{O\textsubscript{2}} could, however,
explain the decrease in $S_\text{O}_2$ seen after administration of nor-
epinephrine and phenylephrine because these drugs do not affect CBF. On the other hand, administration of ephedrine does not affect $S_\text{O}_2$ but its effect on extra- and intra-cerebral perfusion is unknown. The hypothesis of the present study was that not only CBF but also external carotid and skin blood flow are maintained with the use of ephedrine. Furthermore, we took advantage of using two SR-NIRS machines to evaluate whether a large detector separation attenuates the influence of extracranial flow on $S_\text{O}_2$, accepting that such a comparison involves the undisclosed algorithms used by the apparatus to derive at $S_\text{O}_2$.

**Methods**

Ten healthy males (age 20–54 yr; height 175–180 cm; weight 74–102 kg) participated in the study that was approved by the local ethics committee [H-4-2010-132 (35774)] and conducted in accordance with the Declaration of Helsinki including the subjects’ written and oral consent.

First the subjects were familiarized with the experimental setting and then positioned in a hospital bed for 20 min before catheterization. Under local anaesthesia (2% lidocaine), a catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted in the right internal jugular vein by the Seldinger technique and advanced to the subclavian vein above the supraorbital edge over each hemisphere. The sensors were placed laterally 2–3 cm from supraorbital cutaneous blood flow and the frontal sinuses, sensors were placed 1.5 cm from the carotid bifurcation for ICA and ECA while blood flow in VA was determined between the transverse process of the C3 vertebra and the subclavian artery. We used the brightness mode to measure mean vessel diameter in a longitudinal direction and cross section. The Doppler velocity spectrum was subsequently identified by pulsed wave mode. The systolic and diastolic diameters were measured and the mean diameter was taken as [(systolic diameter $\times$ 0.5) + (diastolic diameter $\times$ 2/3)]. The time-averaged mean flow velocity obtained in pulsed wave mode was measured by tracing average flow for each time phase and by calculating the time-averaged value across $\approx 45$ cardiac cycles to eliminate the effects of ventilation. When recording blood flow velocity, care was taken to ensure that probe position was stable, that insonation angle did not vary and was smaller than 60°, and that sample volume was focused at the centre of the vessel and covered its width. Mean blood flow velocity was calculated on the basis of velocity waveforms traced by the apparatus software. Flow was the cross-sectional area [$\pi \times (0.5 \times$ mean diameter)$^2$] times mean blood flow velocity: blood flow $\times \pi \times (0.5 \times$ mean diameter)$^2$ which has an accuracy of 5%. Furthermore, from the temporal ultrasound sound window, blood flow velocity in the middle cerebral artery (MCAvmean) was determined by transcranial Doppler sonograph (2 MHz probe, Multi-Dop, DWL, Singen, Germany) with the best signal-to-noise ratio obtained at a depth of 44–56 mm, and the probe was secured by a headband.

**Protocol**

After catheterization, subjects rested supine for 30 min. Before infusion of either phenylephrine or ephedrine control measures were obtained for 15 min. Since the effect of ephedrine is prolonged while the effect of phenylephrine lasts for only minutes, administration was in a fixed order with phenylephrine (50 μg ml$^{-1}$; 1–1.75 mg per subject; n=9) administered first. After 90 min ephedrine (1 mg ml$^{-1}$; 50–135 mg; n=9) was administered when cardiovascular variables had returned to the basal level. Administration of the two drugs was titrated to achieve an $\approx 20$ mm Hg increase in MAP.

After 12–14 min of drug infusion, blood samples were obtained in pre-heparinized syringes, and were immediately analysed for arterial oxygen and carbon dioxide tension ($P_{\text{AO}_2}$, $P_{\text{ACO}_2}$) and oxygen saturation ($S_{\text{O}_2}$, $S_\text{O}_2$) (ABL700; Radiometer, Copenhagen, Denmark). We used an arterial to venous derived estimate of cerebral oxygenation ($S_{\text{AVO}_2}$):

$$S_{\text{AVO}_2} = S_{\text{O}_2} \times 0.25 + S_{\text{J}O_2} \times 0.75.$$
During administration of ephedrine plasma catecholamines were determined to evaluate to what extent ephedrine influences plasma norepinephrine. Arterial blood was collected at the end of the infusion while control samples were from a separate day. Samples were immediately centrifuged for 5 min at 3000 rpm and placed in a −80°C freezer. Plasma norepinephrine was determined by high-performance liquid chromatography with electrochemical detection, using an amperometric detector (Antec Decade, Leiden, The Netherlands). The output was recorded on a computer (LCsolution, Simatzhu Corporation, Kyoto, Japan) and used to calculate the area under the curve.

Hyperventilation

To test whether SR-NIRS was sensitive to changes in frontal lobe tissue oxygenation, four subjects were asked to hyperventilate to reduce $P_{aCO_2}$ by 2 kPa. After 3–4 min, $P_{aCO_2}$ and $P_{aO_2}$ were determined.

Statistical analysis and data extraction

On the basis of a previous study, the sample size of a paired $t$-test was indicated to be $n=6$ ($\beta=0.9$) to detect a change in $S_aO_2$ of 8.6 (4.6)% observed with hypoxaemia in healthy humans. Differences between control and either phenylephrine or ephedrine were evaluated using a paired $t$-test in proc mixed SAS 9.2 (SAS Institute, Inc., Cary, NC, USA) with a significance level set to $P<0.05$. Averages were calculated over 60 s for each intervention at steady-state. The distribution of the raw data (i.e. mean, median, and skewness) was controlled by proc univariate in SAS, and the data are presented as absolute changes from baseline [standard deviation (SD)] in Table 1 and Figure 1, and in Figure 2 as relative changes from baseline (95% confidence interval).

Results

Flow in carotid artery could not be obtained with a sufficient signal in one subject. Furthermore, one subject did not receive phenylephrine while ephedrine was not administered to another subject due to problems with the central catheter. Measurements of SkBF and $S_{skin}O_2$ during administration of phenylephrine were excluded for two subjects due to signal error probably because the sensor was not secured.

Phenylephrine

The MAP and TPR increased by 16 and 6 mm Hg min litre$^{-1}$, respectively, and SV increased along with a reduction in HR (Table 1; $n=10$). Phenylephrine reduced $S_{foreO_2}$ and $S_{invos}O_2$ by 6.9 (95% confidence interval: 4.8–9.0%; $P<0.0001$) and 10.5 (8.2–12.9%; $P<0.0001$; $n=9$), but $S_aO_2$ and $S_{skin}O_2$ ($n=8$) were not affected significantly (Fig. 1). Phenylephrine also reduced ECAf by 17 (6–28%; $P=0.0001$; $n=7$) but increased ICAf by 13 (5–21%; $P=0.003$) leaving VAf, MCAvmean, and SkBF unchanged (Fig. 2 and Table 1).

Ephedrine

There was an increase in MAP, CO, and HR by 18 mm Hg, 1.5 litre min$^{-1}$, and 12 bpm, respectively, and TPR was reduced by
4 mm Hg min litre⁻¹ (Table 1; n=10). The $S_{\text{Sfore}}O_2$ and $S_{\text{skin}}O_2$ were not changed while $S_{\text{invos}}O_2$ (0.7–4.5%; $P=0.017$; n=9) and $S_{\text{av}}O_2$ (0.5–3.3%; $P=0.012$; n=10) decreased (Fig. 1).

With ephedrine ICAf and VAf did not change, but ECAf increased by 11% (4–18%; $P=0.005$) (Fig. 2; n=7). MCAvmean and SkBF were maintained, but ephedrine provoked a slight
decrease in $P_{aCO_2}$ ($P=0.003$). Plasma norepinephrine increased from 4.7 (1.0) to 23.6 (7.5) nM ($P=0.004$).

**Hyperventilation**

There was a reduction in $P_{aCO_2}$ by 2.9 kPa and $S_{AVO_2}$ was reduced by 16.9% ($P=0.018$), $S_{foreO_2}$ by 4.7% ($P=0.02$), and $S_{invosO_2}$ by 7.4% ($P=0.023$) with $S_{skinO_2}$ remaining stable. Thus, the 'CO$_2$ reactivity' was 1.6% kPa$^{-1}$ for Foresight and 2.6% kPa$^{-1}$ for Invos, but these values were not significantly different ($P=0.2$).

**Discussion**

The important finding of this study is that ephedrine increased ECAF without affecting ICAF or VAF, or MCA$_{V_{mean}}$. The SR-apparatus applied here aims to suppress influence from extra-cerebral blood flow albeit by use of different sensor-configurations.$^{24}$ Yet, both Foresight and Invos-5100c failed to reflect only oxygenated blood within cerebral tissue, although they were sensitive to reduction in an arterial to jugular influence on cardiac preload. 27 In supine healthy humans, ephedrine might have a different impact on CO depending on its eventual contribution to cerebral oxygenation, 39 the impact of vasopressors on the NIRS signal should be addressed. 25 Thus, it is important to rule out the effect of vasopressors on the NIRS signal when 'time of cerebral deoxygenation' is used (e.g. for comparison of control and intervention groups). 5, 7, 34 Commercially available SR-NIRS apparatus often claims to provide an absolute value for cerebral oxygenation, but even in homogenous tissue such as skeletal muscle the absolute value provided by SR-NIRS is disputed. 40 However, changes in $S_{O_2}$ seem more important for interpretation of oxygen delivery. 39

The penetration depth for light is proportional to the emitter–detector distance (1 of 3 to 1 of that distance). 41 The Invos has a 4 cm distance from the emitter to the detector, whereas the Foresight device employs 5 cm and should therefore reach more brain tissue. The detector–detector distances are 1 cm (Invos) and 3.5 cm (Foresight), but although Foresight employs both a large penetration depth and detector–detector separation, $S_{foreO_2}$ was reduced during administration of phenylephrine. An emitter–detector separation of 4 cm should be sufficient to reach the brain from the forehead in healthy subjects 52 but might not be in (elderly) patients presenting cerebral atrophy. Also, oxygenation of blood in subcutaneous tissue and the skull remains to be quantified for eventual contribution to $S_{O_2}$, and we assumed that they are correlated with ECAF and $S_{skinO_2}$.

The wavelengths used for SR-NIRS often include about 810 mm to address the isobestic point where O$_2$Hb and HHb have similar absorptivity. Some SR-NIRS machines utilize several wavelengths to improve accuracy or to allow calculation of additional components, 43 here exemplified by the Foresight that uses four wavelengths while Invos uses only two. Yet, the Foresight demonstrated a 'CO$_2$ reactivity' of only 1.6% kPa$^{-1}$ compared with 2.6% kPa$^{-1}$ for the Invos and, to our surprise, the Foresight system appeared to have a lower sensitivity to changes in both extracranial and brain oxygenation than the Invos.

**Limitations**

We have addressed some limitations of the Foresight and Invos-5100c. The algorithms and assumption made by the SR-machines applied here are not disclosed, which limits a thorough sensitivity profile. If SR-NIRS is to report oxygenated haemoglobin within the brain only, the optimal emitter–detector separation, the wavelengths, and perhaps integration of white light spectroscopy to exclude a superficial contribution to $S_{O_2}$ should be addressed. We did not observe significant reduction in $S_{skinO_2}$ and SkBF during administration of
phenylephrine, possibly attributable to movement of the sensor causing large sds. However, we believe that extra-cerebral blood flow was reduced with phenylephrine as demonstrated by ECAF. We used a fixed 25:75 ratio as a reference for SR-NIRS26 albeit the optimal reference might depend on both extra-cerebral blood flow and cerebral blood volume.27 Also, the administered sympathomimetic agents might affect brain microcirculation28 and we did not perform a CO₂-correction with the use of ephedrine.

Conclusion

The results indicate that a larger penetration depth and additional wavelengths do not necessarily attenuate an extra-cerebral contribution to SR-NIRS-derived S₂O₂. Thus, phenylephrine increases internal carotid blood flow and S₂O₂ is reduced as external carotid blood flow decreases. On the other hand, ephedrine increases cerebrovascular resistance by reducing Paco₂, but S₂O₂ is largely maintained because of an increase in external carotid blood flow.

Authors’ contributions


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Declaration of interest

None declared.

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