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

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Editor's key points

- Cerebral oxygenation monitors are used to follow cerebral perfusion and guide fluid and vasopressor therapy, but are subject to extracerebral influences.
- The effects of phenylephrine, ephedrine, and hyperventilation on cerebral oxygenation were studied in healthy volunteers using two monitors of cerebral oxygenation.
- Phenylephrine increased and ephedrine maintained internal carotid artery flow, while cerebral oxygenation was unchanged because of extracerebral perfusion influences.

Background. Phenylephrine and ephedrine affect frontal lobe oxygenation (S_cO_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_cO_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 ($S_{av}O_2$) 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. Invos-5100c ($S_{invos}O_2$) and Foresight ($S_{fore}O_2$) determined S_cO_2 while forehead skin oxygenation ($S_{skin}O_2$) was assessed.

Results. Phenylephrine reduced $S_{fore}O_2$ by 6.9% (95% confidence interval: 4.8–9.0%; $P<0.0001$), $S_{invos}O_2$ 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 $S_{skin}O_2$ or $S_{av}O_2$. In contrast, $S_{fore}O_2$ was maintained with administration of ephedrine while $S_{invos}O_2$ and $S_{av}O_2$ 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 $S_{skin}O_2$ did not change.

Conclusions. The effect of phenylephrine on S_cO_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_cO_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_cO_2) can be monitored by near infrared spectroscopy (NIRS), and S_cO_2 identifies the lower limit of cerebral autoregulation[3] and can be used to guide so-called individualized goal-directed fluid therapy.[4] Perioperative optimization of S_cO_2 carries the potential to improve postoperative outcomes in cardiac[5 6] and elderly patients,[7] while a low preoperative S_cO_2 might predict adverse postoperative outcomes.[8] S_cO_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_cO_2 by emphasizing light returning from 'deep' tissues.[10]

In both awake and anaesthetized humans, an influence of extracranial tissue oxygenation on S_cO_2 could, however,

explain the decrease in S_cO_2 seen after administration of norepinephrine[11] and phenylephrine[12–14] because these drugs do not affect CBF.[15 16] On the other hand, administration of ephedrine does not affect S_cO_2 but its effect on extra- and intra-cerebral perfusion is unknown.[12 13] 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_cO_2, accepting that such a comparison involves the undisclosed algorithms used by the apparatus to derive at S_cO_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 its bulb.[17] The position of the catheter was verified by an auditory response with quick infusion of saline and eventually by nociception related to the mastoid process.[18] A catheter (1.1 mm, 20 G) was inserted in the brachial artery of the non-dominant arm, and a third catheter (Cavafix MT134, Braun, Melsungen, Germany) was advanced to the subclavian vein from a cubital vein and used for drug administration. Catheters were connected to a transducer (Edwards Life Sciences, Irvine, CA) placed at the level of the heart (5 cm below the sternum). From the transducer the catheters were connected to a monitor (Dialogue-2000 IBC-Danica Electronic, Denmark) for determination of mean arterial pressure (MAP) and heart rate (HR). Stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were derived according to Modelflow® technology (BeatScope; Finapres Medical System BV, Amsterdam, The Netherlands) taking weight, height, age, and gender into account.[19] Data were analogue-digital converted and sampled at 100 Hz (Powerlab, ADInstruments, Colorado Springs, CO, USA).

Two SR-NIRS systems (Invos-5100c, Covidien, Mansfield, MA, USA and Foresight, CAS Medical Systems, Inc., Branford, CT, USA) assessed S_cO_2. Invos-5100c uses an emitter–detector distance of 3 and 4 cm and light at 730 and 808 nm, whereas Foresight applies emitter–detector separation of 1.5 and 5 cm and uses light at 690, 780, 808, and 850 nm. To avoid influence from supraorbital cutaneous blood flow and the frontal and sagittal sinuses, sensors were placed laterally 2–3 cm above the supraorbital edge over each hemisphere.[20 21] The sensors for the two devices were placed on the right or left side in randomized order.

Skin oxygen saturation ($S_{skin}O_2$) and blood flow (SkBF) were assessed close to the hairline by an integrated optode (VMS-OXY and VMS-LDF1, Moor Instruments, Axminster, UK) based on white light spectroscopy (400–650 nm) and laser Doppler flowmetry (785 nm) that is influenced by changes in tissue oxygenation and flow to a depth of 1–2 mm within an area of ~9 mm^2. The apparatus has a reported accuracy of 2% and 10 PU for $S_{skin}O_2$ and SkBF, respectively.

Blood flow in the right internal (ICAf) and blood flow in external carotid (ECAf) ($n=8$) and vertebral arteries (VAf) ($n=6$) were examined in randomized order by duplex ultrasonography (Vivid-i, GE Healthcare, Tokyo, Japan). Blood flow was examined ~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 × 1/3)] + [(diastolic diameter × 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 ~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 60 × mean blood flow velocity (cm s^{-1}) × area (cm^2),[22] which has an accuracy of 5%.[23] Furthermore, from the temporal ultrasound window, blood flow velocity in the middle cerebral artery ($MCAv_{mean}$) 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 ~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 (Pa_{O_2}, Pa_{CO_2}) and oxygen saturation (Sa_{O_2}, S_jO_2; ABL700; Radiometer, Copenhagen, Denmark). We used an arterial to venous derived estimate of cerebral oxygenation ($S_{aV}O_2$)[24]:

$$S_{aV}O_2 = Sa_{O_2} \times 0.25 + S_jO_2 \times 0.75.$$