Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects?

P. Brassard*, T. Seifert and N. H. Secher

Department of Anaesthesia, The Copenhagen Muscle Research Centre, Rigshospitalet 2041, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark

*Corresponding author. E-mail: patrice.brassard@gmail.com

Background. Vasopressor agents are commonly used to increase mean arterial pressure (MAP) in order to secure a pressure gradient to perfuse vital organs. The influence of norepinephrine on cerebral oxygenation is not clear. The aim of this study was to evaluate the impact of the infusion of norepinephrine on cerebral oxygenation in healthy subjects.

Methods. Three doses of norepinephrine (0.05, 0.1, and 0.15 μg kg⁻¹ min⁻¹ for 20 min each) were infused in nine healthy subjects [six males; 26 (6) yr, mean (SD)]. MAP, cerebral oxygenation characterized by frontal lobe oxygenation (ScO₂) and internal jugular venous oxygen saturation (SjvO₂), middle cerebral artery mean flow velocity (MCA Vmean), cardiac output (CO), and arterial partial pressure for carbon dioxide (Paco₂) were evaluated.

Results. MAP increased from 88 (79–101) [median (range)] to 115 (98–128) mm Hg with increasing doses of norepinephrine (P < 0.05), reflecting an increase in total peripheral resistance [20.3 (12.2–25.8) to 25.2 (16.4–28.5) mm Hg min litre⁻¹; P < 0.05] since CO remained at baseline values. ScO₂ and SjvO₂ decreased with increasing doses of norepinephrine, reaching statistical significance with norepinephrine infused at 0.1 μg kg⁻¹ min⁻¹ [ScO₂: 78 (75–94) to 69 (61–83)%; P < 0.05; SjvO₂: 67 (8) to 64 (7)%; P < 0.01]. MCA Vmean was reduced with each dose of norepinephrine [56.9 (11.2) to 55.0 (11.7) cm s⁻¹; P < 0.05] and Paco₂ lowered from 5.4 (0.4) to 5.1 (0.4) kPa (P < 0.001).

Conclusions. This study suggests that infusion of norepinephrine at 0.1 μg kg⁻¹ min⁻¹ or higher may negatively affect cerebral oxygenation.


Keywords: arterial pressure, drug effects; brain, blood flow; sympathetic nervous system, norepinephrine

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When vital organ perfusion pressure is challenged, for example, in response to anaesthesia or septic shock, one approach of securing perfusion pressure is provided by the use of vasopressor agents such as phenylephrine, ephedrine, and norepinephrine. Depending on their specific target, some agents will exclusively influence vascular resistance as others will have additional chronotropic, inotropic, or both properties. Although the impact of sympathomimetic drugs on mean arterial pressure (MAP) is unequivocal, the consequence of augmenting MAP by elevating vascular resistance or cardiac output (CO) on blood flow and oxygenation of the brain is less clear.

Agents that increase MAP by elevating total peripheral resistance, such as phenylephrine, have been associated with an increase and no change in cerebral vascular resistance. Although an increase in cerebral blood flow (CBF) has been reported in animals and humans with administration of phenylephrine, CBF seems unaffected in some cases. On the other hand, ephedrine increases MAP mainly by elevating CO, but has no influence on middle cerebral artery mean flow velocity (MCA Vmean) in healthy subjects. The latter has been attributed to the absence of an increase in zero flow pressure (ZFP), defined as the MAP extrapolated to an emarginated zero CBF as an expression of arterial tone in the absence of change in intracranial cerebral pressure, and no change in the estimated cerebral perfusion pressure (eCCP) with ephedrine.
The influence of norepinephrine, an \( \alpha \)-agonist, on cerebral haemodynamics is ambiguous. Norepinephrine has been reported to have no influence on eCPP and to elevate ZFP.\(^9\) The CBF may be unaffected by the administration of norepinephrine\(^{10} \) or there may be a small reduction in CBF.\(^{11} \) The influence of norepinephrine on cerebral oxygenation has not been investigated, and the aim of this study was to evaluate the impact of the infusion of different doses of norepinephrine on cerebral oxygenation at rest in healthy subjects. We hypothesized that cerebral oxygenation would be lowered with the infusion of norepinephrine compared with a control saline infusion and that this reduction would be dose-dependent.

**Methods**

The study was approved by the Regional Ethics Committee (H-A-2008-056). Nine healthy volunteers [six males; 27 (7) yr, 1.76 (0.07) m, and 74 (12) kg; mean (sd)] participated in this study after providing their written informed consent. The subjects did not suffer from any medical conditions nor were they taking medications. No restriction on diet or physical activity before the study was provided to the subjects.

Upon their arrival to the laboratory, the subjects were placed on a hospital bed tilted slightly head-down. Under local anaesthesia (lidocaine 2%) and guided by ultrasound, a catheter (1.6 mm; ES-04706, Arrow International, PA, USA) was inserted retrograde in the right internal jugular vein and advanced to its bulb. In two female subjects, we abstained from inserting a catheter in the internal jugular vein since the ultrasound image revealed an unusually small vessel diameter (<3 mm) on both sides of the neck because a vasovagal episode was provoked.

A second catheter (1.1 mm) was inserted in the left brachial artery and a third catheter (0.7 mm) was inserted in the left subclavian vein through an arm vein for the administration of norepinephrine. After catheterization, the subjects were placed supine and they rested for 1 h before the norepinephrine was infused to offset the nociceptive stimuli associated with catheterization.

The frontal lobe oxygenation (\( S_{\text{O}_2} \)) was monitored by near-infrared spectroscopy (NIRS) (INVOS Cerebral Oximeter, Somanetics, Troy, MI, USA), which determines the absorption of near-infrared light at 703 and 808 nm and reports an index of the ratio of oxyhaemoglobin to total haemoglobin. The NIRS optodes are designed with one light-emitting diode and two separate optodes whereby changes in light absorption relate predominantly to total haemoglobin in blood vessels positioned deeper than the skin and the skull.\(^{12} \) The optodes were attached as high as possible on the forehead to avoid the frontal sinuses and they were covered to shield external light.\(^{13} \)

Changes in CBF velocity were identified by MCA Vmean through the posterior temporal ultrasound window with transcranial Doppler sonography using a 2 MHz probe (Multidop X, DWL, Sipplingen, Germany).\(^{14} \) After obtaining the optimal signal-to-noise ratio, the probe was fixed by adhesive ultrasonic gel (Tensive, Parker Laboratories, Orange, NJ, USA) and secured by a headband.

Considering that the utilization of vasopressors aims at increasing cerebral perfusion pressure (CPP) via an increase in MAP, it is of clinical interest to quantify CPP. However, the traditional means of measuring CPP and intracranial pressure are invasive, including an arterial line and a subarachnoid or intracranial catheter. Accordingly, the use of a non-invasive method of estimating CPP is of interest. eCPP, representing the area under the pulsatile amplitude of the flow velocity and arterial pressure waveforms, was derived from:\(^{15} \)

\[
eCPP = \frac{\text{MCA Vmean}}{\text{MCA Vmean} - \text{MCA Vdiast}} \times (\text{MAP} - \text{DAP})
\]

where MCA Vdiast is the diastolic middle cerebral artery flow velocity and DAP the diastolic arterial pressure.

ZFP, which mainly represents cerebral vascular tone assuming that the subjects have no elevated intracranial pressure and considered to be the effective downstream pressure, was calculated as:

\[
\text{ZFP} = \text{MAP} - \text{eCPP}
\]

Arterial and venous blood samples were simultaneously obtained at time points 0, 10, and 20 min during the infusion, and results were calculated based on the last 10 min of observation. Blood samples were purged from any atmospheric content and immediately analysed for jugular venous oxygen saturation (\( S_{\text{O}_2} \)) and arterial and venous pressures for carbon dioxide (\( P_{\text{aCO}_2} \) and \( P_{\text{vCO}_2} \), respectively) using an ABL 725 (Radiometer, Copenhagen, Denmark).

Haemodynamic monitoring included MAP, heart rate (HR), stroke volume (SV), and CO. The MAP was measured through a transducer (Edwards Life Sciences, Irvine, CA, USA) placed at the level of the heart and connected to a monitor (Dialogue-2000 IBC-Danica Electronic, Denmark) with sampling at 100 Hz (Di-720, Dataq, OH, USA) for offline analysis of HR and CO. Beat-to-beat SV was estimated from the arterial pressure wave according to the Modelflow method.\(^{16} \) This method uses a non-linear three-element model of the aortic input impedance and simulates aortic flow waveforms from a peripheral arterial pressure signal. Two of the three model elements, that is, aortic characteristic impedance and arterial compliance, depend on the aorta’s elastic properties and are computed using a built-in database of artangent aortic pressure–area relationship given the age, height, weight, and gender of the subject under investigation.

Integrating the aortic flow waveform per beat provides left ventricular SV, and CO is computed by multiplying SV and HR. The third model element, peripheral vascular
Results

The MAP increased from 88 (79–101) to 115 (98–128) mm Hg with increasing doses of norepinephrine (P < 0.05 for 0.1 and 0.15 μg kg⁻¹ min⁻¹) and reflected an increase in total peripheral resistance [20.3 (12.2–25.8) to 25.2 (16.4–28.5) mm Hg min litre⁻¹; P < 0.05] since CO remained at the baseline value (Table 1, Fig. 1). This increase in MAP led to an elevation in eCPP (P < 0.05 for 0.1 and 0.15 μg kg⁻¹ min⁻¹), and also in pulse pressure and ZFP for the highest dose (P < 0.05).

The ScCO₂ and SyvO₂ lowered with increasing doses of norepinephrine, reaching statistical significance at 0.1 μg kg⁻¹ min⁻¹ and higher [ScCO₂: 78 (75–94) to 69 (61–83)%; P < 0.05; SyvO₂: 67 (8) to 64 (7)%; P < 0.01]. The MCA Vmean was reduced with each dose of norepinephrine [56.9 (11.2) to 55.0 (11.7) cm s⁻¹; P < 0.05]. Finally, PαCO₂ lowered with increasing doses of norepinephrine [5.4 (0.4) to 5.1 (0.4) kPa; P < 0.001] whereas PvCO₂ did not change from baseline values.

### Table 1

| Infusions of norepinephrine are in μg kg⁻¹ min⁻¹. MAP, mean arterial pressure; eCPP, estimated cerebral perfusion pressure; PP, pulse pressure; ZFP, zero flow pressure; TPR, total peripheral resistance; saline: ScCO₂, arterial pressure CO₂ and SyvO₂, arterial pressure vCO₂; *P < 0.05, †P < 0.01, ‡P < 0.001 vs saline.

<table>
<thead>
<tr>
<th>Infusions</th>
<th>MAP (mm Hg)</th>
<th>eCPP (mm Hg)</th>
<th>PP (mm Hg)</th>
<th>ZFP (mm Hg)</th>
<th>TPR (mm Hg)</th>
<th>ScCO₂ (%)</th>
<th>SyvO₂ (%)</th>
<th>MCA Vmean (cm s⁻¹)</th>
<th>PαCO₂ (kPa)</th>
<th>PvCO₂ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>saline</td>
<td>88 (79–101)</td>
<td>84.6 (69–95)</td>
<td>54 (41–61)</td>
<td>6 (9)</td>
<td>67 (8)</td>
<td>56.9 (11.2)</td>
<td>67 (8)</td>
<td>55.0 (11.7)</td>
<td>5.4 (0.4)</td>
<td>5.3 (0.4)</td>
</tr>
<tr>
<td>0.05</td>
<td>100 (83–109)</td>
<td>100.6 (83–121)</td>
<td>50 (46–69)</td>
<td>7 (12)</td>
<td>64.7 (9)</td>
<td>55.0 (11.7)</td>
<td>67 (8)</td>
<td>55.0 (11.7)</td>
<td>5.4 (0.4)</td>
<td>5.3 (0.4)</td>
</tr>
<tr>
<td>0.10</td>
<td>108 (84–124)</td>
<td>108.6 (84–127)</td>
<td>50 (46–69)</td>
<td>8 (12)</td>
<td>64.8 (9)</td>
<td>55.0 (11.7)</td>
<td>67 (8)</td>
<td>55.0 (11.7)</td>
<td>5.4 (0.4)</td>
<td>5.3 (0.4)</td>
</tr>
<tr>
<td>0.15</td>
<td>115 (98–128)</td>
<td>115.6 (98–132)</td>
<td>50 (46–69)</td>
<td>9 (12)</td>
<td>64.8 (9)</td>
<td>55.0 (11.7)</td>
<td>67 (8)</td>
<td>55.0 (11.7)</td>
<td>5.4 (0.4)</td>
<td>5.3 (0.4)</td>
</tr>
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Discussion

The present results suggest that although the infusion of nor-epinephrine increases MAP by peripheral vasoconstriction in a dose–response manner, leading to an elevation in eCPP, it also negatively affects cerebral oxygenation, characterized by a reduction in both \( \text{ScO}_2 \) and \( \text{SjvO}_2 \), reaching a statistical significant reduction in this study with the infusion of 0.1 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) or higher dose.

The maintenance of an adequate perfusion is important for vital organs such as the brain. On the basis of the studies reporting no impact or only a small reduction in CBF with administration of norepinephrine,\(^{10,11}\) the elevation of CPP in situations during which the brain perfusion is challenged has been thought to be safely undertaken by increasing MAP. However, the influence of norepinephrine on cerebral haemodynamics is ambiguous. Strebel and colleagues\(^{20}\) reported an increase in MCA \( \text{Vmean} \) after the administration of norepinephrine titrated to increase MAP 20% above baseline value, but suggested that in these anaesthetized patients, the augmentation in MCA \( \text{Vmean} \) was influenced by the effect of the anaesthetic agents on cerebral autoregulation. In order to rule out the impact of anaesthesia on cerebral autoregulation, Moppett and colleagues\(^9\) gradually infused 0.02–0.1 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) of norepinephrine to awake healthy subjects and increased MAP by 25% with no change in MCA \( \text{Vmean} \). This observation was explained by an increase in cerebrovascular tone expressed as ZFP, resulting in no change in eCPP. In the present study, the infusion of 0.1 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) of norepinephrine increased MAP by \( \sim 23\% \) leading to an elevation in eCPP without significantly increasing cerebrovascular tone expressed as ZFP, but in contrast to the findings by Moppett and colleagues, it lowered MCA \( \text{Vmean} \). Increasing the dose of norepinephrine to 0.15 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) produced similar results except that ZFP also increased. This reduction in MCA \( \text{Vmean} \) could be considered small, but since cerebral vasculature possess sympathetic innervation,\(^{21}\) it may be that the infusion of norepinephrine had a direct vasoconstrictor effect on the MCA, transiently increasing MCA \( \text{Vmean} \) and thus, underestimating the reduction in CBF. However, whether changes in MCA \( \text{Vmean} \) represent changes in CBF with infusion of norepinephrine remains to be proven.

The novel finding of the present study is the reduction in cerebral oxygenation after the infusion of norepinephrine to healthy subjects. The infusion of 0.1 and 0.15 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) of norepinephrine led to a reduction of \( \sim 8\% \) and \( \sim 3\% \) in \( \text{ScO}_2 \) and \( \text{SjvO}_2 \), respectively, and a 10–15% reduction in \( \text{ScO}_2 \) is associated with presyncopal symptoms.\(^{22}\) Although the spectrometer is spatially resolved, the lower reduction in \( \text{SjvO}_2 \) compared with \( \text{ScO}_2 \) could be related to a diminution in skin blood flow from the frontal area measured by the NIRS apparatus after the infusion of norepinephrine. As \( \text{ScO}_2 \), mainly reflects the venous compartment, we could expect that a reduction in \( \text{ScO}_2 \) represents to some extent a reduction in \( \text{SjvO}_2 \), especially with an arterial oxygen saturation most likely stable in healthy subjects. Furthermore, the concomitant reductions in three flow-related signals, for example, MCA \( \text{Vmean} \), \( \text{ScO}_2 \) and \( \text{SjvO}_2 \), suggest that cerebral oxygenation...
was impaired with the infusion of norepinephrine. The preservation of cerebral oxygenation, during surgery, for example, is of importance since an association has been reported between a reduction in ScO₂ with early postoperative neurological dysfunction in patients undergoing cardiopulmonary bypass surgery, although the clinical relevance of such a reduction in ScO₂ on the neurological function in other types of surgeries or in healthy subjects is presently unknown.

The influence of norepinephrine on arterial chemoreceptors could partly explain the reduction in cerebral oxygenation. Administration of norepinephrine increases the arterial chemoreceptor discharge, which in turn, elevates pulmonary ventilation. This increase in pulmonary ventilation reduces PaCO₂, leading to cerebral vasoconstriction and subsequent lowering in CBF and eventually cerebral oxygenation. In the present study, PaCO₂ decreased in response to increasing doses of norepinephrine, reaching statistical significance with the two highest doses of norepinephrine. The infusion of 3.0 μg min⁻¹ of norepinephrine led to a reduction in internal carotid artery blood flow in patients with an intracranial pathology but with normal cerebrospinal fluid pressure, in whom a reduction in PaCO₂ was present.

ScO₂ depends on CBF, cerebral metabolic ratio for oxygen, arterial oxygen content, and haemoglobin concentration. It may be that the reduction in ScO₂, with infusion of norepinephrine, assuming constant CBF, arterial oxygen content, and haemoglobin concentration, represents an increase in the cerebral metabolic ratio for oxygen, even though subjects were awake and presumably their state of arousal was constant. However, we have demonstrated that there were no statistically significant changes in oxygen-to-glucose index (oxygen/glucose) or oxygen-to-carbohydrate index (oxygen/glucose+½ lactate) with increasing doses of norepinephrine in healthy subjects.

The absence of increase in CO after the infusion of norepinephrine may also be associated with this reduction in cerebral oxygenation. Ogoh and colleagues reported a linear relationship between CO and MCA Vmean at rest and during exercise. Of note, the ability to augment CBF during exercise becomes limited in clinical populations in which CO does not increase, such as in patients with chronic heart failure. However, CBF and ScO₂ increase during exercise in healthy subjects. In situations during which a low CO is encountered like in haemorrhagic shock, a lowered CBF at a given MAP is present compared with the induction of hypotension with sympatholytic drugs. Taken together, these results suggest that the ability of CO to increase together with MAP is important for the preservation of MCA Vmean and cerebral oxygenation. Sympathetic activity could be triggered by a reduction in SV or pulse pressure detected by the baroreceptors, but it seems that this was not the case as both SV and pulse pressure increased with the infusion of norepinephrine.

There were large individual variations in the NIRS-derived ScO₂, and we consider changes in ScO₂ more important than the absolute values. However, the concomitant reduction in three parameters of flow, for example, ScO₂, ScvO₂, and MCA Vmean, together strongly suggest a reduction in CBF. A confirmation of these results is needed, for example, with the use of functional magnetic resonance that also measures the balance between deoxyhaemoglobin and oxyhaemoglobin, to evaluate the regional distribution of CBF. The use of a method based upon pulse wave analysis to evaluate CO could be considered a problem during interventions which may influence systemic vascular resistance, impedance, and compliance of the vascular system, but it has been clinically validated under such circumstances. Further research is warranted (i) to establish if the reduction in PaCO₂ after the infusion of norepinephrine is the main contributor to the reduction in cerebral oxygenation; (ii) to evaluate the residual impact of norepinephrine, that is, when the infusion is stopped, on cerebral oxygenation; and (iii) to evaluate the clinical consequences of a reduction in cerebral oxygenation, more specifically, the impact of the amplitude and the length of the reduction, on neurological function.

In conclusion, the results of this study suggest that although the infusion of norepinephrine elevates MAP and eCPP, it negatively affects cerebral oxygenation at a dose of 0.1 μg kg⁻¹ min⁻¹ and higher.

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