Effect of Phenylephrine and Ephedrine Bolus Treatment on Cerebral Oxygenation in Anaesthetized Patients

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Abstract and Introduction

Abstract

Background How phenylephrine and ephedrine treatments affect global and regional haemodynamics is of major clinical relevance. Cerebral tissue oxygen saturation (\(SctO_2\))-guided management may improve postoperative outcome. The physiological variables responsible for \(SctO_2\) changes induced by phenylephrine and ephedrine bolus treatment in anaesthetized patients need to be defined.

Methods A randomized two-treatment cross-over trial was conducted: one bolus dose of phenylephrine (100–200 µg) and one bolus dose of ephedrine (5–20 mg) were given to 29 ASA I–III patients anaesthetized with propofol and remifentanil. \(SctO_2\), mean arterial pressure (MAP), cardiac output (CO), and other physiological variables were recorded before and after treatments. The associations of changes were analysed using linear-mixed models.

Results The CO decreased significantly after phenylephrine treatment \([\Delta CO=−2.1 (1.4) \text{ litre min}^{-1}, P<0.001]\), but was preserved after ephedrine treatment \([\Delta CO=0.5 (1.4) \text{ litre min}^{-1}, P>0.05]\). The \(SctO_2\) was significantly decreased after phenylephrine treatment \([\Delta SctO_2=−3.2 (3.0)\% , P<0.01]\) but preserved after ephedrine treatment \([\Delta SctO_2=0.04 (1.9)\% , P>0.05]\). CO was identified to have the most significant association with \(SctO_2(P<0.001)\). After taking CO into consideration, the other physiological variables, including MAP, were not significantly associated with \(SctO_2(P>0.05)\).

Conclusions Associated with changes in CO, \(SctO_2\) decreased after phenylephrine treatment, but remained unchanged after ephedrine treatment. The significant correlation between CO and \(SctO_2\) implies a cause–effect relationship between global and regional haemodynamics.

Introduction

Phenylephrine and ephedrine are routinely used in the perioperative setting to treat anaesthesia-related hypotension in order to maintain mean arterial pressure (MAP) and cerebral perfusion pressure.\(^1\) However, phenylephrine and ephedrine have very different pharmacological effects: phenylephrine is a pure \(\alpha_1\)-agonist, whereas ephedrine is a mixed-acting agent with positive inotropic and chronotropic effects.\(^2\) Indeed, the distinctive effects of phenylephrine and ephedrine on global haemodynamics (such as cardiac output, CO)\(^3\) and regional haemodynamics (such as cerebral tissue oxygen saturation, \(SctO_2\))\(^4\) have been demonstrated.
Recently published studies show that near-infrared spectroscopy (NIRS)-guided brain protection protocols in cardiac surgery might lead to reduced neurocognitive complications and improved postoperative outcomes.\(^5\) Because the endpoint of haemodynamic optimization is to improve oxygen delivery, monitoring cerebral oxygenation may help to elucidate the effects of various clinical interventions on global and regional haemodynamics.\(^6\) Moreover, several studies have demonstrated that changes in $S_c tO_2$ correlate with changes in cerebral blood flow (CBF) when cerebral metabolic rate of oxygen (CMRO$_2$) and arterial blood oxygen content are kept constant.\(^7\) Understanding how the administration of phenylephrine and ephedrine affects cerebral perfusion and oxygenation is of major clinical relevance because both agents are routinely used to treat anaesthesia-related hypotension in surgical patients.

Consequently, the aims of our study were (i) to investigate the effect of phenylephrine and ephedrine bolus administration on cerebral oxygenation in anaesthetized patients and (ii) to identify the physiological variables [MAP, CO, heart rate (HR), stroke volume (SV), end-tidal $CO_2$ ($E_{CO_2}$), oxygen saturation via pulse oximetry ($SP_O_2$), and bispectral index (BIS)] which are responsible for the changes in $S_c tO_2$ induced by phenylephrine and ephedrine treatments.

**Discussion**

This study demonstrates that concordant with changes in CO, cerebral oxygenation ($S_c tO_2$) significantly decreased after phenylephrine bolus treatment and remained unchanged after ephedrine bolus treatment, even though MAP was significantly increased by both agents. Among all physiological variables being considered (MAP, CO, HR, SV, $E_{CO_2}$, $SP_O_2$, and BIS), CO was identified as the variable associated most significantly with $S_c tO_2$. The other variables (MAP, HR, SV, and $E_{CO_2}$) which associated significantly with $S_c tO_2$ became insignificant after taking CO into consideration.

Cerebral oxygenation is determined by oxygen delivery to the brain and oxygen consumption by the brain (CMRO$_2$). Oxygen delivery to the brain depends on cerebral perfusion (CBF) and arterial blood oxygen content. Studies have shown that changes in $S_c tO_2$ correlate with changes in CBF if CMRO$_2$ and arterial blood oxygen content are kept constant.\(^7\) In the present study, we considered CMRO$_2$ to be constant because our patients were under general Anaesthesia and the infusion rates of propofol and remifentanil were kept constant. Moreover, in order to achieve stable blood propofol and remifentanil concentrations, we waited for at least 10 min between starting TIVA and giving the first pressor treatment. We also considered arterial blood oxygen content to be constant because there was no surgical haemorrhage and no sign of desaturation. Therefore, we submit that the observed changes of $S_c tO_2$ in this study were mainly caused by changes in CBF.

The importance of arterial pressure management in patients undergoing anaesthesia has been substantiated by the significant relationship between intraoperative hypotension and postoperative neurocognitive impairment.\(^{12}\) Despite the fact that arterial pressure monitoring is a standard practice, consensus in terms of when and how to treat intraoperative hypotension is still lacking. Among all options, phenylephrine and ephedrine belong to the set of typical sympathomimetic agents routinely chosen to increase arterial pressure.\(^2\) However, little is known about the impacts of these agents on cerebral oxygenation and the relationship between global and regional
haemodynamics. If treating hypotension is an attempt to avoid organ ischaemia and hypoxia, we are actually achieving the opposite result (decreased cerebral oxygenation) by administering phenylephrine, as demonstrated in this study using a quantitative NIRS device and in previous studies using a trend NIRS device. Another study also demonstrated the negative impact of norepinephrine infusion on cerebral oxygenation. Thus, the routine and indiscriminate use of vasopressors might be less beneficial than previously thought. Nonetheless, prospective and randomized studies are needed to address whether the negative impact of vasopressor treatment on \( SctO_2 \) relates to adverse patient outcomes, especially because recent studies have suggested that low \( SctO_2 \) values are related to poor postoperative outcome. In contrast, ephedrine's \( SctO_2 \)-preserving ability is reassuring. However, studies are again needed to demonstrate whether or not the administration of ephedrine rather than phenylephrine relates to a better outcome.

The mechanism of how phenylephrine administration leads to a decreased cerebral oxygenation is intriguing. It has been found that sympathetic nerve activity (SNA) originating from the superior cervical ganglion increases promptly after pharmacologically (including phenylephrine) induced rapid increase in arterial pressure. Considering that the cerebral vasculature is largely innervated by the superior cervical ganglion, we speculate that phenylephrine bolus treatment may constrict cerebral resistance vessels indirectly via reflexively increased SNA to the brain. This assertion is supported by the findings that cerebral arteries are abundantly innervated by sympathetic nerve fibres and that both \( \alpha \) - and \( \beta \) -adrenoceptors are demonstrated in the vascular walls in the brain. It is also supported by the finding that stellate ganglion block leads to a decreased cerebral vascular tone. Nonetheless, the discussion over whether or not SNA affects cerebral perfusion and oxygenation has lasted for more than 100 yr, witnessed by the recently well-organized point–counterpoint debate. It should be noted that direct action of either phenylephrine or ephedrine on cerebral resistance vessels is practically nil since we know that vasoactive amines do not cross the blood–brain barrier.

To the best of our knowledge, this study is the first one to demonstrate a significant relationship between global haemodynamics (CO) and regional haemodynamics \( (SctO_2) \) in situations where CO changes are induced by sympathomimetic agents in anaesthetized patients. The distinctive effects of phenylephrine and ephedrine on \( SctO_2 \) are thus explained by their distinctive impacts on CO. Our data concur with previous reports that a reduced CO correlates with decreased cerebral haemodynamics, despite maintained MAP in situations where CO changes are induced by preload swing in healthy non-anaesthetized volunteers. The mechanism behind the modulation of cerebral haemodynamics by CO is believed to be sympathetically mediated vasoconstriction consequent to a reduced CO. This assertion is supported by the finding that dynamic inputs from CO and SV are important in the regulation of baroreflex control of muscle SNA in healthy, normotensive humans. Alternatively, the influence of CO on cerebral haemodynamics may depend on circulating blood volume distribution rather than autonomic control. Consequently, our study emphasizes the relationship between global and regional haemodynamics and supports the importance of studies focusing on this relationship as well as studies evaluating the impact of regional haemodynamics on patients’ outcome. Our finding also supports the emerging practice of goal-directed haemodynamic optimization because optimized global haemodynamics is related to a minimized risk of regional ischaemia and hypoxia.
Interestingly, our data showed that the difference in $SctO_2$ changes was significant between the first and second phenylephrine treatments ($P<0.01$) and not significant between the first and second ephedrine treatments ($P=0.19$) based on unpaired Student’s $t$-test. These results suggest that the effect of phenylephrine treatment on cerebral haemodynamics is negated by the previous ephedrine treatment. In contrast, the effect of ephedrine treatment is less affected by phenylephrine. This finding may be caused by the longer clinical half-life of ephedrine than phenylephrine (clinical observation). Our analysis of the carry-over effect based on linear-mixed models showed that this is not significant ($P=0.11$) at the 0.05 level. This might be due to the fact that testing carry-over effects usually requires a larger sample size than that of our study.

The main methodological considerations are as follows. The method of phenylephrine and ephedrine administration in this study was bolus, not infusion. The effects of bolus and infusion administrations on systemic and cerebral haemodynamics may be different. For example, the gradual increase in MAP caused by infusion might not be able to elicit the same increase in SNA in the superior cervical ganglion as that seen with bolus. A comparison study between bolus and infusion would be informative. Secondly, we used $SctO_2$ based on NIRS measurements to assess cerebral haemodynamics. Middle cerebral artery flow velocity ($MCA_v$) based on transcranial Doppler (TCD) measurement, which is also non-invasive and portable, is another technology being used for the same purpose. However, $MCA_v$ may not provide a valid CBF estimation should vessel calibre or flow profile change.\textsuperscript{[29]} Indeed, in studies where both technologies were adopted, it was found that $MCA_v$ increased, whereas $SctO_2$ decreased after phenylephrine bolus and infusion administration in healthy non-anaesthetized volunteers.\textsuperscript{[11, 13]} One of the possible explanations for this discrepancy lies in the fact that TCD measures flow velocity in large cerebral arteries, whereas NIRS measures oxygen saturation mainly at the capillary bed.

In summary, associated with the changes in CO, cerebral oxygenation decreases after phenylephrine but remains unchanged after ephedrine bolus treatment in anaesthetized patients, even though both agents consistently increase MAP. The significant correlation between CO and $SctO_2$ implies a cause–effect relationship between global haemodynamics (CO) and regional haemodynamics ($SctO_2$).

**Supplementary Material**

Supplementary material is available at British Journal of Anaesthesia online.

**Sidebar**

**Editor’s Key Points**

- Effects of different vasopressor agents on cerebral oxygenation have been unclear.
- Ephedrine and phenylephrine, used for intraoperative hypotension, were investigated in a cross-over design study.
- Phenylephrine, but not ephedrine, decreased cardiac output (CO) and brain oxygenation.
This study highlights the importance of CO in preserving brain oxygenation during management of intraoperative hypotension.