Effect of phenylephrine on the haemodynamic state and cerebral oxygen saturation during anaesthesia in the upright position

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Background. The upright sitting or beachchair position is associated with hypotension, and potential risk of cerebral hypoperfusion and cerebral injury. We hypothesized that by increasing arterial pressure with phenylephrine administration, cerebral perfusion, and postoperative recovery would be improved.

Methods. Thirty-four patients undergoing elective shoulder surgery were randomized to receive either saline or phenylephrine infusion (PE) 5 min before being placed in the upright position. Simultaneous measurements of mean arterial pressure, cerebral oxygen saturation, middle cerebral artery velocity, and cardiac function using transthoracic echocardiography were made. Postoperative neurocognitive function was assessed.

Results. At the commencement of PE, mean (SD) cerebral oxygen saturation significantly decreased from 77 (10) to 67 (13)% (P=0.02), and further to 59 (11) % on upright positioning. The level of cerebral saturation upright was not significantly different to patients receiving saline (P=0.07), with values remaining at room-air levels. Middle cerebral artery blood velocity increased by 20% (P=0.04). Phenylephrine prevented hypotension in the upright position primarily by maintaining preload and increasing systemic vascular resistance (P=0.01), and was associated with a decrease in cardiac output. No postoperative neurocognitive dysfunction was identified.

Conclusions. Despite maintaining arterial pressure with phenylephrine, cerebral desaturation occurred with upright positioning. Cerebral oxygen saturation can provide a valuable endpoint when evaluating the effect of vasopressor therapy on cerebral perfusion.

Keywords: complications, cerebral ischaemia; monitoring, echocardiography; oxygen, saturation; position, sitting; sympathetic nervous system, phenylephrine

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The placement of patients into the upright position for shoulder surgery is commonly associated with hypotension, and potential risk of cerebral hypoperfusion and cerebral injury. Elevation of the head during anaesthesia is particularly relevant for elderly patients with hypertensive or cerebrovascular disease, as an elevated lower limit of cerebral autoregulation can predispose them to cerebral ischaemia. Even though this risk of ischaemic-related neurological injury is undefined, reported complications are often related to errors in arterial pressure measurement. A recent recommendation relating to upright positioning, is that arterial pressure should be maintained close to pre-induction values, to preserve cerebral perfusion, and thereby reduce any risk of cerebral injury or postoperative cognitive dysfunction.

With hypotension induced by the upright sitting position, both intracranial blood flow velocity, and cerebral oxygen saturation (ScO2) are reported to decrease. Cerebral oximetry monitors tissue hypoxia and provides a therapeutic endpoint for vasopressor therapy, to optimize cerebral oxygen delivery, and improve postoperative outcome. Further a protracted cerebral oxygen desaturation is associated with neurocognitive impairment and mortality.
We hypothesized that prophylactic administration of phenylephrine, an alpha-adrenoceptor agonist, would attenuate hypotension associated with the upright position, maintain cerebral perfusion, and prevent postoperative neurocognitive dysfunction. This is particularly relevant as cerebral oxygen saturation has been reported to decrease with phenylephrine administration.\textsuperscript{15} Our aim was to investigate the effect of phenylephrine on the circulation, and correlate this with changes in cerebral perfusion, by measurement of middle cerebral artery flow velocity and cerebral oxygen saturation. We also wanted to assess the effect on postoperative neurocognitive recovery. By using an integrative approach, the systemic effects of phenylephrine could be discerned from effects within the cerebral circulation.

**Methods**

Following approval by our institutional Ethics Committee and trial registration (Australian and New Zealand Clinical Trials Registry 12610001075077), informed written consent was obtained from 34 patients undergoing elective shoulder arthroscopy in the upright position. Patients were excluded if there was a history of cerebrovascular event, significant cardiac disease (New York Heart Association symptoms class 3, or pacemaker), carotid endarterectomy, contraindications to interscalene block, or a body mass index (BMI) of $>35$. Patients were randomized to two groups according to a computer-generated random numbers table: Group 1 received general anesthesia with saline infusion (S), Group 2 general anesthesia with phenylephrine infusion (PE). A standardized sevoflurane general anesthetic technique, combined with interscalene brachial plexus anesthesia, was used in all patients.

On arrival in the operating theatre, patients received warmed Hartmann’s solution 15 ml kg\textsuperscript{-1} i.v. and were sedated with midazolam 0.05 mg kg\textsuperscript{-1}. Interscalene brachial plexus anesthesia was performed under ultrasound guidance, using 0.75% ropivacaine (30–35 ml). The radial artery was directly cannulated for continuous arterial pressure monitoring. The transducer was positioned at the level of the tragus throughout surgery to reflect cerebral perfusion pressure. Near-infrared spectroscopy (NIRS) optode sensors (INVOS Somanetics, Troy, MI, USA) were placed bilaterally on each forehead 1–2 cm above the brow, and sensor edges taped to prevent interference from ambient light. Cerebral oxygen saturation ($S_{\text{O}_2}$) was measured as an average of left and right frontal readings which in all cases remained within 5% of each other. Systemic pulse oximetry, ECG, and bispectral index monitoring (BIS, Aspect Medical Systems, Newton, MA, USA) was applied.

$S_{\text{O}_2}$ and haemodynamic variables were measured with patients inspirating room air ($F_{\text{IO}_2}$) 0.21, and after pre-oxygenation ($F_{\text{IO}_2}$ 0.5). General anesthesia was induced with fentanyl (1 $\mu$g kg\textsuperscript{-1}), propofol (1.5–2.0 mg kg\textsuperscript{-1}) and atracurium (0.5 mg kg\textsuperscript{-1}), and the trachea intubated. Patients were ventilated with oxygen and air ($F_{\text{IO}_2}$ 0.5) and end-tidal carbon dioxide maintained at 4.7–5.3 kPa. Anaesthesia was maintained with sevoflurane, with end-tidal sevoflurane concentration maintained around 1.5%, targeting for a BIS value 40–60. Temperature was continuously monitored via a nasopharyngeal temperature probe.

After haemodynamic stabilization, Transcranial Doppler (TCD) and transthoracic cardiac measurements were made (Fig. 1), with the echocardiographer blinded to patient randomization. Mean arterial pressure (MAP), heart rate (HR), end-tidal carbon dioxide, end-tidal sevoflurane and BIS were continuously recorded. Patients then received an infusion of either phenylephrine (1.5 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1}) or normal saline at equal rate, a regime recommended by Ngan Kee and colleagues.\textsuperscript{11} Following 5 min of infusion TCD measurement of middle cerebral artery velocity (MCAv) was repeated. Patients were then immediately placed into a steep upright position, with head elevation $>75\textdegree$. The head was positioned in a neutral position to facilitate venous drainage, usually 3–5 min, after which repeat transthoracic and TCD measurements were made.

A protracted decrease ($>5$ min) in MAP to $<60$ mm Hg, was treated with metaraminol 500 $\mu$g bolus, and/or atropine 300 $\mu$g bolus if bradycardia (HR $<45$) was present. A further criterion for intervention was a significant decrease in $S_{\text{O}_2}$ ($>25$% decrease below baseline, or absolute value $<50\%$).

**Transthoracic echocardiography**

A portable ultrasound unit with a 5–1 MHz phased array transducer (P21x) was used (M-turbo, Sonosite, Sydney, Australia). Measurements included parasternal long-axis views of left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD), and left ventricular outflow tract diameter (LVOT\textsubscript{D}).\textsuperscript{12} Left ventricular outflow tract velocity time integral (VTI) was measured using an apical 5-chamber view. Fractional shortening was calculated from the relation $LVEDD–LVESD/LVEDD$. Cardiac output (CO) was calculated from the product of VTI, HR, and LVOT cross-sectional area ($0.785 \pi \cdot LVOT\textsubscript{D}^2$). Cardiac index (CI) and systemic vascular index (SVRI) were derived from the body surface area (BSA): CO/BSA and MAP.BSA/CO, respectively.

**Transcranial doppler**

A 2 MHz phased array transducer was placed over the temporal bone to measure blood flow velocity of the M1 segment of the MCA. A measurement was taken at a horizontal segment 10 mm from the carotid bifurcation using 3 mm wide sample window. The MCA was identified in an oblique axial plane, skewed $10–20\textdegree$ above the horizontal, at a depth of 45–55 mm.\textsuperscript{13} Measurements were taken over a period of three or more cardiac cycles with respiration suspended. The time-averaged mean flow (TAM) was calculated from the spectral waveform.

**Postoperative recovery**

The postoperative quality of recovery scale (PQRS)\textsuperscript{14} is a questionnaire that scores six domains of patient cognitive and overall function. Patients were assessed at time periods after the end of anaesthesia: at 15 min, 40 min,
1 day, 3 days, and 12 weeks. Following hospital discharge data were collected via telephone.

### Statistical analysis

Data are presented as mean (standard deviation). Haemodynamic and echocardiographic variables were compared using repeated measure ANOVA for group vs time interaction. The primary outcome was a change in $S_cO_2$ and power analysis showed a sample size $n=17$ was required to detect a change of 5%, ($SD$ 5.02, alpha of 0.05, and power of 0.8). This was felt to be clinically significant as pre-oxygenation was observed to increase $S_cO_2$ by this magnitude, and upright positioning is associated with decreases in both MAP and $S_cO_2$ of 20%.[11 5–17] Comparison within groups (between post-induction and infusion/post-induction, and upright) used the paired Students t-test. The analysis of PQRS data was via the Cochran–Mantel–Haenszel test.

### Results

A total of 34 patients were recruited, and all were included in the final analysis. Middle cerebral artery velocity measurement was not performed in 3 patients (S: 2, PE: 1) because of poor temporal window imaging. Patient characteristics were similar in both (Table 1). A small number were taking cardioactive medication (S: 4 patients, PE: 4 patients). Anaesthesia was similar in both groups, with no significant difference in surgical time, induction agent dose, end-tidal carbon dioxide and sevoflurane concentrations, BIS value, and temperature (Table 2).

On entry to the operating theatre (Table 3) both patient groups had similar readings of $S_cO_2$ ($P=0.65$). After preoxygenation and induction, $S_cO_2$ increased similarly in both groups ($P=0.38$). Patients who then received PE had a further decrease of 10% in $S_cO_2$ ($P=0.02$) compared with no change in patients receiving S. Upright positioning showed a similar decrease in $S_cO_2$ in both groups (11–12%) from post-infusion values. However, when compared with post-induction values, PE resulted in an $S_cO_2$ decrease of 18% (7% below room air) compared with a reduction of only 11% in untreated patients (no change from room air). The difference in $S_cO_2$ between the groups after upright positioning did not reach significance ($P=0.07$).

In all patients, analysis of left and right hemisphere $S_cO_2$ values showed a mean value was representative of cerebral desaturation, as the difference between left and right values remained similar (<5%) during repeated measurement.

In the saline group intervention with one of more doses of metaraminol was required in 11 patients for hypotension, with MAP 46 (10) mm Hg after upright positioning. The resultant increase in MAP by 24 (8) mm Hg, was associated with an increase in both MCAv by 5.0 (4.1) cm s$^{-1}$ and $S_cO_2$ by 6 (4) %.

No patient in the phenylephrine group required intervention for hypotension, but one patient had a cerebral oxygen

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**Table 1** Patient characteristics. Values are mean (sd). Age mean (range). BMI, body mass index

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>14/3</td>
<td>14/3</td>
</tr>
<tr>
<td>Age</td>
<td>40 (32–48)</td>
<td>47 (37–57)</td>
</tr>
<tr>
<td>Weight</td>
<td>84.3 (10.3)</td>
<td>81.8 (14.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 (3.2)</td>
<td>25.4 (2.8)</td>
</tr>
<tr>
<td>Cuff procedures</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Stability procedures</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Open procedures</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
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**Table 2** Intraoperative details. Values are mean (sd). $\text{E}′_{\text{CO}_2}$, end-tidal carbon dioxide concentration; $\text{E}′_{\text{SEVO}}$, end-tidal sevoflurane concentration; BIS, bispectral index value

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl (mg)</td>
<td>82 (13)</td>
<td>84 (13)</td>
</tr>
<tr>
<td>Midazolam (mg)</td>
<td>3.8 (1.0)</td>
<td>3.7 (0.9)</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>146 (25)</td>
<td>162 (41)</td>
</tr>
<tr>
<td>$\text{E}′_{\text{SEVO}}$ (%)</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.2)</td>
</tr>
<tr>
<td>$\text{E}′_{\text{CO}_2}$ (kPa)</td>
<td>4.8 (0.4)</td>
<td>4.5 (0.5)</td>
</tr>
<tr>
<td>BIS</td>
<td>42 (7)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>35.5 (0.6)</td>
<td>35.5 (0.5)</td>
</tr>
</tbody>
</table>

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**Figure 1** Study protocol for patients randomized to receive either saline or PE before upright positioning. After preoxygenation ($\text{Pre}_O_2$) and anaesthetic induction, a period of haemodynamic stabilization occurred before commencement of infusion, and placement into upright. Echocardiographic and TCD measurements were made before and after positioning.
saturation <50 despite a MAP of 100 mm Hg. Metaraminol was administered without effect, after which increasing to \( F_{\text{O}_2} \) to 1.0 and re-positioning the head increased saturation to >60%.

Following the induction of anaesthesia, middle cerebral artery flow velocity (Table 3) was similar in both groups \((P=0.5)\). PE increased MCAv by 20% (from baseline), compared with no change in patients receiving saline \((P=0.04)\). On upright positioning MCAv remained elevated in the phenylephrine group (23% from baseline), while in the saline group, MCAv decreased significantly from baseline \((P=0.01)\).

MAP was similar in both groups \((P=0.19)\), and after anaesthetic induction arterial pressure decreased similarly in both (28 and 33%, respectively, \(P=0.90)\). After stabilization, PE then caused a significant increase in MAP, returning to before-induction levels, compared with S \((P<0.001)\). On upright positioning a small reduction in MAP still occurred in the phenylephrine group \((11\%)\) compared with a significant decrease in MAP \((25\%)\) in the saline group \((P<0.001)\). Phenylephrine maintained MAP at before-induction levels compared with the significant MAP decrease in untreated patients.

The haemodynamic measurements are shown in Table 4, with change from baseline in Figure 2. CI decreased in both saline and phenylephrine groups on upright positioning \((16 \text{ and } 24\%, \text{ respectively, } P=0.27)\). In the saline group, the decrease in CI was associated with a significantly reduced left ventricular end-diastolic dimension \((P<0.03)\). Bradycardia occurred with PE contributing to a decrease in cardiac output, and persisted during upright positioning \((P<0.01)\). Systemic vascular resistance index decreased on upright positioning, but in contrast, significantly increased in the phenylephrine group \((P<0.01)\). There was no significant difference between groups for fractional shortening or left ventricular end-systolic dimension \((P=0.20, 0.15, \text{ respectively})\).

### Upright

There was no significant difference in the PQRS assessment between groups.

### Discussion

This study has demonstrated that PE is associated with a reduction in cerebral tissue oxygenation during beach chair positioning. Phenylephrine was, however, effective in preventing the decrease in cardiac stroke volume and systemic vascular resistance, the primary cause of hypotension. Cerebral oxygen desaturation occurred at commencement of infusion before upright positioning, indicating a possible direct or indirect vasoconstrictive effect on the cerebral circulation. The observed increase in middle cerebral artery flow velocity is consistent with such a response, and if associated with a reduction in cerebral perfusion, would explain the change in cerebral saturation. Alternatively, a shift in the arterial to venous contribution of the near-infrared signal, used to measure frontal lobe oxygenation, could also explain this decrease in cerebral saturation. A change in venous volume would increase cerebral venous admixture, reduce \(S_{\text{cO}_2}\), but without necessarily decreasing tissue oxygen content.

Upright positioning is commonly associated with hypotension, and associated decreases in \(S_{\text{cO}_2}\) may be interpreted as a decrease in cerebral perfusion with a compensatory increase in oxygen extraction.\(^6\) Other factors may influence

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**Table 3** Cerebral saturation \((S_{\text{cO}_2})\), mean arterial pressure (MAP), and middle cerebral artery velocity (MCAv) in patients during induction of anaesthesia and placement into the upright position. Values are mean \((\text{SD})\), *\(P=0.02\), † \(P=0.04\), ‡ \(P=0.01\) phenylephrine compared with saline.

<table>
<thead>
<tr>
<th>(S_{\text{cO}_2}) (%)</th>
<th>Saline</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>MCAv (cm s(^{-1}))</td>
</tr>
<tr>
<td>Room air</td>
<td>68 (7)</td>
<td>94 (11)</td>
</tr>
<tr>
<td>Preoxygenation</td>
<td>74 (9)</td>
<td>94 (11)</td>
</tr>
<tr>
<td>Post-induction</td>
<td>79 (10)</td>
<td>68 (9)</td>
</tr>
<tr>
<td>Post-infusion</td>
<td>76 (9)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>Upright position</td>
<td>68 (8)</td>
<td>53 (13)</td>
</tr>
</tbody>
</table>

**Table 4** Heart rate (HR), left ventricular end-diastolic dimension (LVEDD), cardiac index (CI), and systemic vascular resistance index (SVRI) in patients during anaesthesia and placement into the upright position. Values are mean \((\text{SD})\), *\(P=0.03\) and † \(P=0.01\) phenylephrine compared with saline.

<table>
<thead>
<tr>
<th>Saline</th>
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<tr>
<td></td>
<td>HR (bpm)</td>
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<tr>
<td></td>
<td>Supine</td>
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<td></td>
<td>Upright</td>
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causing cerebral vasoconstriction. One suggestion is that ically mediated reflex from the superior cervical ganglion, Rapid changes in MAP are postulated to activate a sympathet-
pathways could autoregulate cerebral blood flow in response to and critical closing pressure.

The effect of phenylephrine on the cerebral circulation appears complex, as an increase in cerebral perfusion pressure would be expected to maintain, if not increase \( S_cO_2 \), in the upright position. The human cerebral circulation is richly innervated with adrenergic fibres and cerebral vascular responsiveness to norepinephrine (and sympathomimetics) is mediated primarily by alpha-1 compared with alpha-2 adrenoceptors. However, it has been proposed that phenylephrine does not cross the blood brain barrier. Extracranial pathways could autoregulate cerebral blood flow in response to phenylephrine-induced changes in MAP or cardiac output. Rapid changes in MAP are postulated to activate a sympathetically mediated reflex from the superior cervical ganglion, causing cerebral vasoconstriction. One suggestion is that such reflex activation may have a differential effect on arterial and venous tone, increase cerebral venous blood volume and alter the arterial to venous content measured by NIRS. A limitation of the study is the prophylactic infusion of phenylephrine at a single high concentration to elevate arterial pressure. Our results indicate this concentration is not recommended, as it appears to predispose the cerebral circulation to vasoconstriction. A dose-ranging study could be valuable in identifying which concentration is optimal, in identifying systemic from cerebral vascular effects. The use of \( S_cO_2 \) as an index of brain hypoxia is not without limitation, as the frontal lobes alone were monitored, and other cerebral regions including the vertebro-basilar arterial system, remain unmonitored. TCD is limited in that it measures blood flow velocity rather than flow, and an increase in MCAv is not necessarily an increase in cerebral perfusion. We studied a relatively young and healthy population without significant cardiorespiratory or cerebrovascular disease. Further study in an older population, particularly with cerebrovascular disease is relevant as many elderly patients have underlying cognitive impairment, not readily apparent at preoperative assessment, and later unmasked by surgery.

Our study has shown phenylephrine to elevate arterial pressure during upright surgery, but not prevent the associated decrease in cerebral oxygen saturation with upright positioning. A lower phenylephrine concentration or alternative vasopressor agents may be more suitable in integrating the response between the systemic arterial pressure and cerebral blood flow.

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Declaration of interest
None declared.

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