Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients

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Editor’s key points
- Maintenance of adequate tissue perfusion and oxygenation is important during anaesthesia.
- In patients undergoing cardiopulmonary bypass, the authors independently manipulated blood flow and systemic arterial pressure.
- Cerebral and systemic oxygenation were positively correlated with flow but not with pressure.

Background. Although both pressure and flow are considered important determinants of regional organ perfusion, the relative importance of each is less established. The aim of the present study was to evaluate the impact of variations in flow, pressure, or both on cerebral and whole-body oxygen saturation.

Methods. Thirty-four consenting patients undergoing elective cardiac surgery on cardiopulmonary bypass were included. Using a randomized cross-over design, four different haemodynamic states were simulated: (i) 20% flow decrease, (ii) 20% flow decrease with phenylephrine to restore baseline pressure, (iii) 20% pressure decrease with sodium nitroprusside (SNP) under baseline flow, and (iv) increased flow with baseline pressure. The effect of these changes was evaluated on cerebral \( (\text{ScO}_2) \) and systemic \( (\text{SvO}_2) \) oxygen saturation, and on systemic oxygen extraction ratio (OER). Data were assessed by within- and between-group comparisons.

Results. Decrease in flow was associated with a decrease in \( \text{ScO}_2 \) from 63.5 (7.4) to 62.0 (8.5) %, \( P<0.001 \). When arterial pressure was restored with phenylephrine during low flow, \( \text{ScO}_2 \) further decreased from 61.0 (9.7) to 59.2 (10.2) %, \( P<0.001 \). Increase in flow was associated with an increase in \( \text{ScO}_2 \) from 62.6 (7.7) to 63.6 (8.9) %, \( P=0.03 \), while decreases in pressure with the use of SNP did not affect \( \text{ScO}_2 \), \( \text{SvO}_2 \) was significantly lower (\( P<0.001 \)) and OER was significantly higher (\( P<0.001 \)) in the low flow arms.

Conclusions. In the present elective cardiac surgery population, \( \text{ScO}_2 \) and \( \text{SvO}_2 \) were significantly lower with lower flow, regardless of systemic arterial pressure. Moreover, phenylephrine administration was associated with a reduced cerebral and systemic oxygen saturation.

Keywords: cardiopulmonary bypass; oximetry; phenylephrine; spectroscopy, near-infrared

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Decreases in arterial pressure during anaesthesia are often managed by vasopressor use. However, vasoconstrictors may impair regional organ perfusion, which might go undetected when monitoring solely arterial pressure.\(^5\) Cerebral oximetry, a non-invasive technology using near infra-red spectroscopy (NIRS), enables an estimation of systemic venous oxygen saturation, thereby providing a means for real-time monitoring of adequacy of organ perfusion.\(^2,3\)

In a proposed algorithm to correct for decreases in NIRS-derived cerebral oxygen saturation (\( \text{ScO}_2 \)), increasing mean arterial pressure (MAP) with the use of vasopressors was suggested as one of the initial measures to correct for low \( \text{ScO}_2 \).\(^6\) However, recent published data demonstrated that vasopressors such as phenylephrine may negatively affect \( \text{ScO}_2 \).\(^5\)\(^-\)\(^9\) This negative effect on \( \text{ScO}_2 \) was not observed when increase in arterial pressure was obtained by vasopressor agents which also increase cardiac output, such as ephedrine.\(^5\)\(^6\)\(^10\) Also, studies in healthy subjects demonstrated an increase in \( \text{ScO}_2 \) during exercise,\(^7\)\(^11\) whereas in patients not capable of increasing cardiac output, such as in patients with heart failure, the ability to augment \( \text{ScO}_2 \) during exercise was limited.\(^12\) These data suggest that cardiac output might contribute to the preservation of cerebral oxygenation. However, it should be acknowledged that it is debated whether the distinctive effects of phenylephrine and ephedrine represent genuine differences in \( \text{ScO}_2 \), explained by their distinctive effects on cardiac output,\(^5\)\(^6\) or if the decrease in \( \text{ScO}_2 \) is a measurement artifact because of cutaneous vasoconstriction by vasopressors and the inability of cerebral oximeters to deal with extracranial contamination.\(^13\)
The aim of the present study was to determine the impact of variations in flow, in pressure, and in both variables at the same time on cerebral and whole-body oxygen saturation. We hypothesized that not only pressure, but also flow would have a major contribution in preservation of cerebral and systemic oxygenation.

A major problem in evaluating physiologic processes is that pressure and flow are intertwined and modifications to one also alter the other. Cardiopulmonary bypass (CPB) represents a unique clinical circumstance in which different aspects of perfusion can be modified independently and in a controlled manner. Therefore, we chose CPB as the model to test our hypothesis. To separate the effect of flow and pressure on cerebral and systemic oxygenation, we independently modified these parameters in patients on CPB.

**Methods**

This prospective clinical study was approved by the Institutional Ethics Committee and written informed consent was obtained from all subjects. The trial is registered at ClinicalTrials.gov (NCT01424800). Thirty-four adult patients undergoing elective cardiac surgery (CABG, valve surgery, or both) on moderately hypothermic CPB without blood transfusion were recruited. Patients with history of cerebrovascular disease or significant carotid artery stenosis (>60%) and patients necessitating vasopressor or inotropic therapy before surgery were excluded.

On the morning of surgery, patients were allowed to take their routine medication, except for angiotensin-converting enzyme inhibitors. Patients were premedicated with oral diazepam (5–10 mg). Standard monitoring was used throughout the procedure, including ECG, pulse oximetry, end-tidal oxygen, carbon dioxide and sevoflurane concentrations, bispectral index (BIS), invasive arterial and central venous pressure measurement, and temperature measurement (AS3, Datex, Helsinki, Finland). Arterial pressure was recorded continuously via the right radial artery catheter. Two disposable NIRS sensors were applied on each side of the forehead for continuous registration of $S_{cO2}$ of the corresponding brain hemisphere (INVOS 5100, Somanetics Corporation, Troy, MI, USA). All data were recorded continuously and integrated digitally with the RUGLOOP® software (Demed, Temse, Belgium).

Anaesthesia was induced with fentanyl 5 μg kg$^{-1}$, diazepam 0.1 mg kg$^{-1}$, and rocuronium 1 mg kg$^{-1}$. The lungs were ventilated mechanically with oxygen enriched air (fractional inspired oxygen 0.6) adjusted to keep the end-tidal carbon dioxide ≈ 5 kPa. Anaesthesia was maintained with boluses of fentanyl up to a total dose of 25–35 μg kg$^{-1}$ and sevoflurane at a minimum concentration of 1.5%.

CPB was performed with a roller pump (Stöckert S5, Sorin group, München, Germany) providing non-pulsatile flow. The priming consisted of 1200 ml colloids (Geloplasma®, Fresenius Kabi, Schelle, Belgium), heparin 5000 IU and mannitol 0.5 g kg$^{-1}$. Systemic heparinization maintained an activated clotting time of >480 s. Moderately hypothermic CPB (blood temperature 30 °C) was initiated at flow rates of 2.5 litre min$^{-1}$ m$^{-2}$. During CPB, $P_{aO2}$ and $P_{aCO2}$ were maintained ~25 and 5 kPa, respectively. Arterial blood gases were measured at 37 °C, independent of body temperature (alpha-stat blood gas management). Blood was sampled after 3 min during steady state, 11 and 13. Temperature, $P_{aCO2}$, $P_{aO2}$, haemoglobin (Hb), and sevoflurane concentrations were kept constant during the measurements.

**Interventions**

The study used a randomized cross-over design where the subjects served as their own controls. Subjects were randomly allocated, based on computer generated codes, to start with the flow-related interventions, or with the pressure related interventions. In all subjects, response to variations in flow, in pressure, and to the combined variation of flow and pressure was investigated. With the interventions, a change of 20% in pressure, flow, or both was aimed. Changes in arterial pressure were obtained by the use of vasoactive agents, sodium nitroprusside (SNP) for arterial pressure decrease and phenylephrine for (SNP) for arterial pressure decrease and phenylephrine for (SNP) for arterial pressure decrease and phenylephrine for (SNP) for arterial pressure decrease and phenylephrine for arterial pressure decrease and arterial pressure decrease and arterial pressure increase. Flow was regulated by control of the pump flow.

Baseline (BL) values of MAP, flow, $S_{cO2}$, and systemic oxygen saturation ($S_{vO2}$) were determined at steady state. Steady state was defined as the presence of a stable (<10% change) MAP over a period of 5 min on CPB. After reaching steady state, four different haemodynamic states were simulated: 20% flow decrease (I1), 20% flow decrease with administration of phenylephrine to restore baseline MAP (I2); then haemodynamics were allowed to return to BL values after which SNP was administered until 20% MAP decrease under baseline flow (I3) followed by restoration of baseline MAP by increasing pump flow (I4). The order of variations in pressure and flow was assigned randomly by the use of a computer generated randomization code. Subjects were randomly assigned to undergo first the flow-related interventions and then the pressure related interventions (Group F), or first the pressure related interventions and then the flow-related interventions (Group P).

All changes were sustained for 5 min. In Group F, the sequence of interventions was BL, I3, I4, BL, I1, I2 (Fig. 1). In Group P, the sequence of interventions was BL, I1, I2, BL, I3, I4. In Group P, the sequence of interventions was BL, I3, I4, BL, I1, I2 (Fig. 1). Interventions were separated by a time period of ~2 min for finalizing computer data registration and preparation of the next intervention.

**Outcome variables**

To analyse the effect of changes in flow and pressure on changes in $S_{cO2}$, right and left $S_{cO2}$ were averaged. We calculated both the change in absolute values in $S_{cO2}$, as the relative change in $S_{cO2}$, defined as the percentage difference between the $S_{cO2}$ value at the start of the intervention and the value exactly 5 min later, at the end of the intervention. To evaluate the effect of changes in flow and pressure on whole-body oxygen balance, $S_{vO2}$ was measured, and systemic oxygen delivery (DO$_2$) and oxygen extraction ratio (OER) were calculated according to standard formulae. Arterial oxygen...
content: \[ CaO_2 = 1.34 \times Hb \times S_aO_2 + 0.003 \times P_aO_2, \] where Hb is haemoglobin concentration, \( S_aO_2 \) is arterial blood oxygen saturation, and \( P_aO_2 \) is arterial partial pressure of oxygen. 

\[ DO_2 = Q \times CaO_2, \] where \( Q \) is pump flow. OER \( = (S_aO_2 - S_vO2) / S_aO2 \), where \( S_vO2 \) is venous blood oxygen saturation.

**Statistical analysis**

Lucas and colleagues\(^8\) assessed the influence of pharmacological-induced changes in arterial pressure on cerebral oxygenation, and indicated an absolute change in \( S_cO2 \) of −1.8% per 10 mm Hg change in MAP, with a reduction approximating 14% during the higher range of MAP. In the present protocol, we aimed at a change of 20% in pressure with the interventions. We, therefore, accepted an absolute change in \( S_cO2 \) of 5% with alterations in pressure or flow as a clinically relevant change. Based on the reported mean \( S_cO2 \) of 64% with a SD of 10%,\(^3\) and accepting a two-tailed \( \alpha \) error of 0.05 and a \( \beta \) error of 0.8, 34 patients were calculated to be required.

Statistical analysis was performed using the statistical software SPSS Statistics 20 (SPSS, Inc., Chicago, IL, USA). Distribution of the data was tested for normality using the Shapiro–Wilk test. The assumption of normality was fulfilled and data are presented as mean (range) for age and mean (SD) for all other variables. Comparisons between Group F and Group P were made with Student’s t-test. Variables during the different interventions were compared using repeated measures analysis of variance (ANOVA), with Tukey correction for multiple post hoc comparisons. For each intervention, differences between pre- and post-intervention \( S_cO2 \) values were tested using a paired data Student’s t-test. A value of \( P < 0.05 \) was taken as the level of significance.

**Results**

The flow diagram for the enrolment, study inclusion and data analysis is presented in Figure 2. Nine female and 25 male subjects with an average age of 62 (range 27–87) yr, weight of 80 (16) kg, and height of 171 (9) cm were enrolled in the study. Patient characteristics did not differ between the F and the P groups.

Temperature, sevoflurane concentrations, \( P_aO_2 \), \( P_aCO_2 \), and haemoglobin showed no differences between the different interventions, nor between the F and the P groups (Table 1).

The intended targets of changes in flow and MAP were reached in all subjects (Table 2). The changes in MAP and flow were not different between the F and the P groups (Table 2), indicating that the sequence of interventions did not bias the data. Therefore, in order to analyse the effect of changes in flow and pressure, we pooled the data of both groups.

The changes in MAP and flow with their concomitant effects on \( S_cO2 \) are illustrated in Figure 3. The changes in \( S_cO2 \) and...
systemic oxygen balance parameters between the interventions are displayed in Table 3.

Responses to decrease in flow

**Intervention 1**

With 20% flow decrease, MAP decreased from 65 (9) to 60 (11), indicating the accompanying decrease in MAP with flow decrease. $\text{ScO}_2$ decreased from 63.5 (7.4) to 62.0 (8.5) %, $P<0.001$ (Fig. 3). Decreases in $\text{ScO}_2$ were significantly more pronounced compared with interventions with normal (I3) and high flow (I4) (Table 3). $\text{SvO}_2$ was significantly lower ($P<0.001$) and OER was significantly higher ($P<0.001$) compared with baseline and compared with interventions with normal and high flow (Table 3).

**Intervention 2**

With 20% flow decrease and administration of phenylephrine to restore baseline arterial pressure, MAP increased from 57 (10) to 70 (8). $\text{ScO}_2$ decreased from 61.0 (9.7) to 59.2 (10.2) %, $P<0.001$ (Fig. 3). Decreases in $\text{ScO}_2$ were significantly more pronounced compared with interventions with normal (I3) and high flow (I4) (Table 3). $\text{SvO}_2$ was significantly lower ($P<0.001$) and OER was significantly higher ($P<0.001$) compared with baseline and compared with interventions with normal and high flow (Table 3).

Responses to decrease in pressure

**Intervention 3**

With 20% MAP decrease [from 66 (12) to 57 (7)], obtained by administration of SNP while maintaining baseline pump flow, $\text{ScO}_2$ did not change significantly [61.7 (8.4)–62.6 (8.4) %, $P=0.13$] (Fig. 3). $\text{SvO}_2$ was significantly higher and OER was significantly lower in conditions with low arterial pressure obtained by SNP (I3) compared with low arterial pressure caused by low flow (I1) (Table 3).

Responses to increase in flow

**Intervention 4**

When increasing pump flow until restoration of baseline MAP [from 61 (11) to 67 (8)], the increase in flow was 11% [from 4.5 (0.5) to 5.0 (0.5) litre min$^{-1}$]. $\text{ScO}_2$ increased from 62.6 (7.7) to 63.6 (8.9) %, $P=0.03$ (Fig. 3). $\text{SvO}_2$ values were not different between conditions with high flow and baseline pressure (I4) compared with baseline flow and low pressure by SNP (I3) (Table 3). $\text{SvO}_2$ was significantly higher and OER was
significantly lower compared with conditions with low flow (I1 and I2) (Table 3).

**Discussion**

The debate on the best strategies for prevention of perfusion deficit and the resulting end organ failure is ongoing. Both pressure and flow are considered important variables. However, the relative importance of each is less established. Under the conditions of the present study, changes in flow affected cerebral and systemic oxygen balance more than changes in MAP. $\text{ScO}_2$ and $\text{SvO}_2$ were significantly lower and OER was significantly higher in the low flow arms, regardless of systemic arterial pressure.

In the elective cardiac surgery population, used in this study, maintaining flow and thus DO$_2$ seemed to be more important than maintaining pressure. This finding is in accordance with data demonstrating that organ injury can be prevented by targeting DO$_2$ levels above a critical threshold during cardiopulmonary bypass. However, the obtained results do not exclude perfusion pressure as an important variable. It is important to note that even during low pressure, our lowest value is higher than the critical value of 50 mm Hg as reported in other studies.

In the present study, increasing arterial pressure with phenylephrine-induced a decrease in $\text{ScO}_2$. This is in accordance with a number of recently published studies. The mechanism of this phenomenon is still unknown. Cardiac output has been proposed as the most important factor in preserving $\text{ScO}_2$. However, in our study pump flow was kept constant during administration of phenylephrine, indicating that other factors than cardiac output or pump flow contribute to the decrease in $\text{ScO}_2$. Some authors relate the decrease in $\text{ScO}_2$ with phenylephrine to direct $\alpha-1$ adrenergic receptor.

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**Table 1** Blood temperature, sevoflurane concentration, and blood gas values during the different interventions, demonstrating no differences between the interventions, nor between the F group (flow-related interventions were performed before the pressure related interventions) and the P group (pressure related interventions were performed before the flow-related interventions). Data are presented as mean (SD). $P$-value between F and P groups >.05; $P$-value between interventions >.05. BL, baseline; I1, 20% flow decrease; I2, 20% flow decrease with administration of phenylephrine to restore baseline MAP; I3, baseline flow with administration of SNP until 20% MAP decrease; I4, restoration of baseline MAP by increasing pump flow; $\text{Pao}_2$, arterial partial pressure of oxygen; $\text{Paco}_2$, arterial partial pressure of carbon dioxide; Hb, haemoglobin.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>I1</th>
<th>I2</th>
<th>I3</th>
<th>I4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ($^\circ$C)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>F group</td>
<td>30.5 (1.3)</td>
<td>30.7 (1.4)</td>
<td>31.0 (1.1)</td>
<td>30.7 (1.3)</td>
<td>30.7 (1.3)</td>
</tr>
<tr>
<td>P group</td>
<td>30.0 (1.5)</td>
<td>30.1 (1.2)</td>
<td>30.2 (1.6)</td>
<td>30.3 (1.4)</td>
<td>30.5 (1.4)</td>
</tr>
<tr>
<td>Sevo (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>F group</td>
<td>1.1 (0.5)</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.5)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>P group</td>
<td>1.0 (0.3)</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.7)</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>$\text{Pao}_2$ (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F group</td>
<td>33 (9)</td>
<td>30 (5)</td>
<td></td>
<td>30 (6)</td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>30 (7)</td>
<td>28 (7)</td>
<td></td>
<td>27 (7)</td>
<td></td>
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<tr>
<td>$\text{Paco}_2$ (kPa)</td>
<td></td>
<td></td>
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<tr>
<td>F group</td>
<td>5.8 (0.5)</td>
<td>5.5 (0.6)</td>
<td></td>
<td>5.7 (0.2)</td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>5.6 (0.6)</td>
<td>5.0 (0.6)</td>
<td></td>
<td>5.0 (0.5)</td>
<td></td>
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<tr>
<td>Hb (g dl$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F group</td>
<td>9.8 (0.9)</td>
<td>9.9 (1.1)</td>
<td></td>
<td>10.1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>9.5 (1.4)</td>
<td>10.0 (1.2)</td>
<td></td>
<td>9.5 (1.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Endpoints of changes in flow and pressure during the different interventions, indicating that the intended targets of changes in flow and pressure were reached in all subjects. Data are presented as mean (SD). $P$-value between F and P groups >.05; $P$-value between interventions <.001. BL, baseline; I1, 20% flow decrease; I2, 20% flow decrease with administration of phenylephrine to restore baseline MAP; I3, baseline flow with administration of SNP until 20% MAP decrease; I4, restoration of baseline MAP by increasing pump flow; MAP, mean arterial pressure.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>I1</th>
<th>I2</th>
<th>I3</th>
<th>I4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow (litre min$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F group</td>
<td>4.5 (0.5)</td>
<td>3.6 (0.4)</td>
<td>3.6 (0.4)</td>
<td>4.5 (0.5)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>P group</td>
<td>4.4 (0.4)</td>
<td>3.6 (0.3)</td>
<td>3.6 (0.3)</td>
<td>4.4 (0.4)</td>
<td>4.9 (0.5)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F group</td>
<td>67 (5)</td>
<td>57 (8)</td>
<td>69 (8)</td>
<td>57 (7)</td>
<td>65 (8)</td>
</tr>
<tr>
<td>P group</td>
<td>70 (9)</td>
<td>63 (9)</td>
<td>71 (9)</td>
<td>57 (7)</td>
<td>68 (8)</td>
</tr>
</tbody>
</table>
activation\textsuperscript{18} or to indirect cerebral vasoconstriction via reflexively increased sympathetic nerve activity.\textsuperscript{19} Others refute this mechanism by stating that the cerebral vasculature lacks significant \(\alpha\) - and \(\beta\)-adrenoceptors.\textsuperscript{20} Recently, it has been suggested that the \(S_c O_2\) decrease with administration of phenylephrine indicates a functional pressure autoregulation mechanism.\textsuperscript{21} The phenylephrine-induced increase in perfusion pressure provokes vasoconstriction of the cerebral arterioles in order to prevent abrupt cerebral hyperperfusion. This mechanism is an indirect myogenic response, because phenylephrine does not cross the blood–brain barrier and cannot constrict cerebral vessels directly.\textsuperscript{22} NIRS calculates the oximetry values based on an assumed cerebral arterial to venous blood volume ratio (A:V ratio).\textsuperscript{23} Autoregulatory vasoconstriction of the cerebral arterioles induces a smaller arterial and relatively larger venous contribution to the NIRS signal, causing a decrease in \(S_c O_2\). This hypothesis is supported by the study of Ogoh and colleagues\textsuperscript{9} who evaluated arterial and venous cerebral blood flow and demonstrated an elevated arterial tone and reduced cerebral venous tone during phenylephrine administration, indicating cerebral autoregulation.

The \(S_c O_2\) increase with SNP-induced hypotension could be readily explained by the same mechanisms. Either nitrates reduce the resistance in the cerebral vessels, allowing more

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**Table 3** \(S_c O_2\) and systemic oxygen balance parameters during the different interventions, demonstrating lower cerebral (\(S_c O_2\)) and systemic (\(S_v O_2\)) oxygen saturation and a higher OER during low flow (I1 and I2) compared with baseline (BL), normal flow (I3), and high flow (I4). Data are presented as mean (SD). *Significantly different from start of intervention. †Significantly different from BL, I3 and I4. ‡Significantly different from BL and I3. I1, 20% flow decrease; I2, 20% flow decrease with administration of phenylephrine to restore baseline MAP; I3, baseline flow with administration of SNP until 20% MAP decrease; I4, restoration of baseline MAP by increasing pump flow. DO\(_2\), oxygen delivery.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>I1</th>
<th>I2</th>
<th>I3</th>
<th>I4</th>
<th>P-value intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S_c O_2) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>63.3 (7.7)</td>
<td>63.5 (7.4)</td>
<td>61.0 (9.7)</td>
<td>61.7 (8.4)</td>
<td>62.6 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End</td>
<td>63.0 (8.6)</td>
<td>62.0 (8.5)*</td>
<td>59.2 (10.2)*</td>
<td>62.6 (8.4)</td>
<td>63.6 (8.9)*</td>
<td></td>
</tr>
<tr>
<td>Relative change in (S_c O_2) (%)</td>
<td>-0.4 (4.2)</td>
<td>-2.8 (3.7)*</td>
<td>-3.2 (3.8)*</td>
<td>1.5 (5.1)</td>
<td>1.6 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DO(_2) (ml min(^{-1}) m(^2))</td>
<td>309 (58)</td>
<td>263 (62)*</td>
<td>320 (63)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(S_v O_2) (%)</td>
<td>86 (3)</td>
<td>82 (4)*</td>
<td>82 (5)*</td>
<td>85 (4)</td>
<td>87 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OER</td>
<td>0.14 (0.03)</td>
<td>0.18 (0.04)*</td>
<td>0.17 (0.05)*</td>
<td>0.14 (0.04)</td>
<td>0.12 (0.04)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
blood flow to the brain, or the $S_{CO_2}$ increase with administration of SNP could be considered as a functional pressure autoregulation mechanism, provoking vasodilation of the cerebral arterioles in order to prevent cerebral hypoperfusion.

It might be argued that the cerebral autoregulation-induced altered A:V ratio accounts for the observed changes in $S_{CO_2}$, without a genuine change in cerebral oxygenation. However, the consistent and concordant changes in both $S_{CO_2}$ and systemic oxygen balance parameters during the different interventions, suggest that $S_{CO_2}$ changes actually reflect oxygen balance changes.

The magnitude of changes in $S_{CO_2}$ in this study was very small (~0.9–1.8% absolute change depending on the intervention) and although statistically significant, the clinical relevance of these changes in the present study may be debatable. However, our results cannot be implicitly extrapolated to any other clinical situation. First, our measurements were done during moderate hypothermia which reduces oxygen consumption, with consequently smaller changes in $S_{CO_2}$. Secondly, we used sevoflurane for maintenance of anaesthesia, which might have blunted the decrease in $S_{CO_2}$ with administration of phenylephrine by its cerebral vasodilatory effect. Based on the same mechanism, the decrease in $S_{CO_2}$ with phenylephrine will be intensified in case of hypocapnia. Thirdly, in the present study, flow and pressure were manipulated within physiological ranges for short periods of time. In clinical practice, larger changes for a longer period are often—deliberately or not—the case.

The results of the present study should be interpreted within the constraints of the methodology. First, to explore the relative contribution of flow and pressure on cerebral oxygenation, and with the aim to separate the effects of both parameters, the present study was performed in patients on CPB where both the flow and the pressure component of perfusion can be modified in a controlled manner. However, as was to be expected, changes in flow were accompanied by changes in pressure (I1 and I4) (Fig. 3). Secondly, based on the principle of spatially resolved spectroscopy, NIRS devices should theoretically distinguish between absorption of photons returning from deep rather than from superficial tissue. However, recently two reports demonstrated that extracranial contamination significantly influences the NIRS signal. Because both vasodilators and vasoconstrictors might affect skin flow directly, changes in skin blood flow might have influenced the NIRS measurements of cerebral oxygenation. It has been suggested that the cerebral oximeter used in the present study is more prone to extracranial contamination. Therefore, administration of vasoactive medication might result in more pronounced artifactual measurements compared with cerebral oximeters with less extracranial contribution. Interestingly, we recently demonstrated that $S_{CO_2}$ responses to acute haemodynamic alterations were also more pronounced when measured with INVOS (Somanetics Corporation, Troy). It is unclear whether this has to be explained by a less accurate measurement technology of INVOS, or whether the other cerebral oximetry devices use a more pronounced signal attenuation technology, resulting in more stable, but less representative, values for both intra- and extracranial measurements.

The clinical significance of the extracerebral contribution in the NIRS signal is not certain. The fact that in the present study the changes in $S_{CO_2}$ were accompanied by changes in $S_{V_O_2}$ and OER, suggests that the changes in $S_{CO_2}$ (both intra- and extracranial) may represent overall tissue perfusion and related oxygen supply and demand ratios, as previously suggested. Thirdly, NIRS measures oxygen saturation in a superficial area of the brain directly below the sensors, but does not examine the deep brain. As recently demonstrated, though a low NIRS value predicts brain hypoperfusion, a normal NIRS value may not always imply that perfusion is adequate. Therefore, the utility of NIRS for individualization of perioperative pressure and blood flow management awaits testing in properly designed and executed clinical trials.

In conclusion, in the elective cardiac surgery population used in this study, changes in flow affected cerebral and systemic oxygen balance more than changes in pressure. Moreover, arterial pressure increase with phenylephrine elicited reduced cerebral and systemic oxygen saturation.

Authors’ contributions
A.M. helped design the study, conduct the study, collect the data, analyse the data, write the manuscript, and approved the final manuscript. W.D. helped conduct the study, collect the data, analyse the data, and approved the final manuscript. F.D. helped design the study, conduct the study, write the manuscript, and approved the final manuscript. P.F.W. helped design the study, write the study, and approved the final manuscript. S.G.D. helped design the study, analyse the data, write the manuscript, and approved the final manuscript.

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Declaration of interest
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