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

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Promotor: Dr. Moerman Anneliese
Co-promotor: Prof. Dr. De Hert Stefan

Masterproef voorgedragen in de master in de specialistische geneeskunde afstudeerrichting Anesthesie en reanimatie
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Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients

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**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 and/or pressure 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, 4 different haemodynamic states were simulated: 1) 20% flow decrease, 2) 20% flow decrease with phenylephrine to restore baseline pressure, 3) 20% pressure decrease with sodium nitroprusside (SNP) under baseline flow, and 4) increased flow with baseline pressure. The effect of these changes was evaluated on cerebral ($S_cO_2$) and systemic ($S_tO_2$) 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 $S_cO_2$ (from 63.5 (7.4) to 62.0 (8.5)%, $p<0.001$). When blood pressure was restored with phenylephrine during low flow, $S_cO_2$ further decreased from 61.0 (9.7) to 59.2 (10.2)%, $p<0.001$. Increase in flow was associated with an increase in $S_cO_2$ 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 $S_cO_2$. $S_tO_2$ 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, $S_cO_2$ and $S_tO_2$ were significantly lower with lower flow, regardless of systemic blood pressure. Moreover, phenylephrine administration was associated with a reduced cerebral and systemic oxygen saturation.

**Keywords:** Cardiopulmonary Bypass; Cerebral Tissue Oxygen Saturation; Oximetry; Phenylephrine; Spectroscopy, Near-Infrared.
Decreases in blood pressure during anaesthesia are often managed by vasopressor use. However, vasoconstrictors may impair regional organ perfusion, which might go undetected when monitoring solely blood pressure. Cerebral oximetry, a noninvasive technology using near infrared spectroscopy (NIRS), enables an estimation of systemic venous oxygen saturation, thereby providing a means for real-time monitoring of adequacy of organ perfusion.

In a proposed algorithm to correct for decreases in NIRS-derived cerebral oxygen saturation (S\textsubscript{c}O\textsubscript{2}), increasing mean arterial pressure (MAP) with the use of vasopressors was suggested as one of the initial measures to correct for low S\textsubscript{c}O\textsubscript{2}. However, recent published data demonstrated that vasopressors such as phenylephrine may negatively affect S\textsubscript{c}O\textsubscript{2}. This negative effect on S\textsubscript{c}O\textsubscript{2} was not observed when increase in blood pressure was obtained by vasopressor agents which also increase cardiac output, such as ephedrine. Also, studies in healthy subjects demonstrated an increase in S\textsubscript{c}O\textsubscript{2} during exercise, whereas in patients not capable of increasing cardiac output, such as in patients with heart failure, the ability to augment S\textsubscript{c}O\textsubscript{2} during exercise was limited. 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 S\textsubscript{c}O\textsubscript{2}, explained by their distinctive effects on cardiac output, or if the decrease in S\textsubscript{c}O\textsubscript{2} is a measurement artifact due to cutaneous vasoconstriction by vasopressors and the inability of cerebral oximeters to deal with extracranial contamination.

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 scheduled for elective cardiac surgery (coronary artery bypass grafting and/or valve surgery) 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 blood 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 $S_o_2$ of the corresponding brain hemisphere (INVOS 5100, Somanetics Corporation, Troy, MI). 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 (ETCO₂) around 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 nonpulsatile 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 seconds. Moderately hypothermic CPB (blood temperature 30 °C) was initiated at flow rates of 2.5 L min⁻¹ m⁻². During CPB, $P_o_2$ and $P_co_2$ were maintained around 25 kPa 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 minutes during steady state, I1 and I3. Temperature, $P_co_2$, $P_o_2$, haemoglobin 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 and/or flow was aimed. Changes in blood pressure were obtained by the use of vasoactive agents, sodium nitroprusside (SNP) for blood pressure decrease and phenylephrine for blood pressure increase. Flow was regulated by control of the pump flow.

Baseline (BL) values of mean arterial blood pressure (MAP), flow, S\textsubscript{c}O\textsubscript{2} and systemic oxygen saturation (S\textsubscript{v}O\textsubscript{2}) were determined at steady state. Steady state was defined as the presence of a stable (<10 % change) MAP over a period of 5 minutes 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 minutes. In group F 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 (Figure 1). Interventions were separated by a time period of about 2 minutes for finalizing computer data registration and preparation of the next intervention.

Outcome variables

To analyze the effect of changes in flow and pressure on changes in S\textsubscript{c}O\textsubscript{2}, right and left S\textsubscript{c}O\textsubscript{2} were averaged. We calculated both the change in absolute values in S\textsubscript{c}O\textsubscript{2}, as the relative change in S\textsubscript{c}O\textsubscript{2}, defined as the percentage difference between the S\textsubscript{c}O\textsubscript{2} value at the start of the intervention and the value exactly 5 minutes later, at the end of the intervention. To evaluate the effect of changes in flow and pressure on whole-body oxygen balance, S\textsubscript{v}O\textsubscript{2} was measured, and systemic oxygen delivery (DO\textsubscript{2}) and oxygen extraction ratio (OER) were calculated according to standard formulae. Arterial oxygen content: C\textsubscript{a}O\textsubscript{2} = 1.34 * H\textsubscript{b} * S\textsubscript{a}O\textsubscript{2} + 0.003 * P\textsubscript{a}O\textsubscript{2}, where H\textsubscript{b} = haemoglobin concentration, S\textsubscript{a}O\textsubscript{2} = arterial blood oxygen.
saturation, \( P_aO_2 \) = arterial blood partial pressure of oxygen. \( DO_2 = Q \times C_aO_2 \), where \( Q \) = pump flow. \( OER = (S_aO_2 - S_vO_2)/S_aO_2 \), where \( S_vO_2 \) = venous blood oxygen saturation.

**Statistical analysis**

Lucas and co-workers assessed the influence of pharmacological-induced changes in blood pressure on cerebral oxygenation, and indicated an absolute change in \( S_cO_2 \) of -1.8 % per 10 mmHg 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 \( S_cO_2 \) of 5 % with alterations in pressure or flow as a clinically relevant change. Based on the reported mean \( S_cO_2 \) of 64 % with a SD of 10 %, 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). 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 \( S_cO_2 \) 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) years, weight of 80 (16) kg and height of 171 (9) cm were enrolled in the study. Demographics did not differ between the F and the P group.

Temperature, sevoflurane concentrations, \( P_aO_2 \), \( P_aCO_2 \) and haemoglobin showed no differences between the different interventions, neither between the F and the P group (Table 1).

The intended targets of changes in flow and MAP were reached in all subjects (Table 2). The changes in flow and MAP were not different between the F and the P group (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_cO_2 are illustrated in figure 3. The changes in S_cO_2 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. S_cO_2 decreased from 63.5 (7.4) to 62.0 (8.5) %, p<0.001 (Fig 3). Decreases in S_cO_2 were significantly more pronounced compared to interventions with normal (I3) and high flow (I4) (Table 3). S_vO_2 was significantly lower (p<0.001) and OER was significantly higher (p<0.001) compared to baseline and compared to interventions with normal and high flow (Table 3).

**Intervention 2:** With 20 % flow decrease and administration of phenylephrine to restore baseline blood pressure, MAP increased from 57 (10) to 70 (8). S_cO_2 decreased from 61.0 (9.7) to 59.2 (10.2) %, p<0.001 (Fig 3). Decreases in S_cO_2 were significantly more pronounced compared to interventions with normal (I3) and high flow (I4) (Table 3). S_vO_2 was significantly lower (p<0.001) and OER was significantly higher (p<0.001) compared to baseline and compared to 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, S_cO_2 did not change significantly (61.7 (8.4) to 62.6 (8.4) %, p=0.13) (Fig 3). S_vO_2 was significantly higher and OER was significantly lower in conditions with low blood pressure obtained by SNP (I3) compared to low blood 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) L min^{-1}). S_cO_2 increased from 62.6 (7.7) to 63.6 (8.9) %, p = 0.03) (Fig 3). S_cO_2 values were not different between conditions with high flow and baseline pressure (I4) compared to baseline flow and low pressure by SNP (I3) (Table 3). S_vO_2 was significantly higher and OER was significantly lower compared to 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. $S_\text{c}O_2$ and $S_\text{v}O_2$ were significantly lower and OER was significantly higher in the low flow arms, regardless of systemic blood pressure.

In the elective cardiac surgery population, used in this study, maintaining flow and thus oxygen delivery ($DO_2$) 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 of 60 mmHg is higher than the critical value of 50 mmHg as reported in other studies.

In the present study increasing blood pressure with phenylephrine induced a decrease in $S_\text{c}O_2$. 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 $S_\text{c}O_2$. 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 $S_\text{c}O_2$. Some authors relate the decrease in $S_\text{c}O_2$ with phenylephrine to direct $\alpha-1$ adrenergic receptor activation or to indirect cerebral vasoconstriction via reflexively increased sympathetic nerve activity. Others refute this mechanism by stating that the cerebral vasculature lacks significant $\alpha$- and $\beta$-adrenoceptors. Recently it has been suggested that the $S_\text{c}O_2$ decrease with administration of phenylephrine indicates a functional pressure autoregulation mechanism. 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, since phenylephrine does not cross the blood-brain barrier and cannot constrict cerebral vessels directly. NIRS calculates the oximetry values based on an assumed cerebral arterial to venous blood volume ratio (A:V ratio). Autoregulatory vasoconstriction of the cerebral arterioles induces a smaller arterial and relatively larger venous contribution to the NIRS signal, causing a decrease in $S_\text{c}O_2$. This hypothesis is supported by the study of Ogoh and colleagues 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.9

The \( S_cO_2 \) increase with SNP-induced hypotension could be readily explained by the same mechanisms. Either nitrates reduce the resistance in the cerebral vessels, allowing more blood flow to the brain,24 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 \( S_cO_2 \). Second, 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.25 26 Based on the same mechanism, the decrease in \( S_cO_2 \) with phenylephrine will be intensified in case of hypocapnia.21 Third, 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 2 reports demonstrated that extracranial contamination significantly influences the NIRS signal.13 27 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 to 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, MI). 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 $S_vO_2$ 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.

Third, 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, blood pressure increase with phenylephrine elicited reduced cerebral and systemic oxygen saturation.
Funding
This work was supported by the Department of Anesthesiology, Ghent University Hospital, Gent, Belgium. The INVOS 5100 cerebral oximeter monitoring system was acquired by a grant from the Belgian Foundation for Cardiac Surgery.

Acknowledgments
Special thanks to our perfusion team (Dirk De Smet, Daniël Dujardin, Martin Vanackere, Korneel Vandewiele) for their skill and dedicated assistance in completing this study.

Declaration of interest
A.M. received lecture fees from Covidien.
Table 1. Blood temperature, sevoflurane concentration, and blood gas values during the different interventions, demonstrating no differences between the interventions, neither 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).

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>I1 (I2)</th>
<th>I3 (I4)</th>
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<tbody>
<tr>
<td><strong>Temp (°C)</strong></td>
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<tr>
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<td>30.7 (1.4)</td>
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<td>30.7 (1.3)</td>
<td>30.7 (1.3)</td>
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<td>30.3 (1.4)</td>
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<td>27 (7)</td>
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<tr>
<td><strong>P_aCO_2 (kPa)</strong></td>
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<td>F group</td>
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<td>5.7 (0.2)</td>
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<td>5.0 (0.5)</td>
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<tr>
<td><strong>Hb (g/dl)</strong></td>
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<tr>
<td>F group</td>
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<td>10.1 (0.9)</td>
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<td>10.0 (1.2)</td>
<td>9.5 (1.3)</td>
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Data are presented as mean (SD). p-value between F and P group > 0.05; p-value between interventions > 0.05. BL: baseline, (I1) 20 % flow decrease, (I2) 20 % flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20 % MAP decrease, (I4) restoration of baseline MAP by increasing pump flow; P_aO_2: arterial blood partial pressure of oxygen, P_aCO_2: arterial blood partial pressure of carbon dioxide, Hb: haemoglobin.
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.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>I1</th>
<th>I2</th>
<th>I3</th>
<th>I4</th>
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</thead>
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<tr>
<td>Flow (L min⁻¹)</td>
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<tr>
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<td>3.6 (0.4)</td>
<td>4.5 (0.5)</td>
<td>5.0 (0.5)</td>
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<tr>
<td>P group</td>
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<td>3.6 (0.3)</td>
<td>3.6 (0.3)</td>
<td>4.4 (0.4)</td>
<td>4.9 (0.5)</td>
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<td>MAP (mmHg)</td>
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<tr>
<td>F group</td>
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<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>

Data are presented as mean (SD). p-value between F and P group > 0.05; p-value between interventions < 0.001. BL: baseline, (I1) 20 % flow decrease, (I2) 20 % flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20 % MAP decrease, (I4) restoration of baseline MAP by increasing pump flow. MAP: mean arterial blood pressure.
Table 3. Cerebral oxygen saturation and systemic oxygen balance parameters during the different interventions, demonstrating lower cerebral ($S_cO_2$) and systemic ($S_vO_2$) oxygen saturation and a higher oxygen extraction ratio (OER) during low flow (I1 and I2) compared to baseline (BL), normal flow (I3), and high flow (I4).

<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>
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<tr>
<td>$S_cO_2$ (%)</td>
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<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</td>
<td>62.6 (8.4)</td>
<td>63.6 (8.9)*</td>
<td></td>
</tr>
<tr>
<td>Relative change</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>in $S_cO_2$ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>$S_vO_2$ (%)</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>

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 sodium nitroprusside until 20 % MAP decrease, (I4) restoration of baseline MAP by increasing pump flow. $DO_2$: oxygen delivery.
### Fig 1

Graphic presentation of the study design. Sequence of interventions in Group F (first the flow related interventions) and Group P (first the pressure related interventions).
**Fig 2** Flow chart presenting the enrolment, study inclusion and data analysis. BL, baseline; CPB, cardiopulmonary bypass; Group F, first the flow related interventions; Group P, first the pressure related interventions.
Fig 3  Mean changes in MAP and flow with their concomitant effects on ScO2 for each intervention. (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 and flow data are presented as mean. ScO2 data are presented as mean and standard error. *P<0.05 between pre- and post-intervention ScO2
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Samenvatting:

Achtergrond: Het hemodynamisch beleid tijdens anesthesie heeft als doel de weefsels van voldoende zuurstof te voorzien. Het is dan ook bewezen dat de klinische uitkomst beter is wanneer de weefselexygenatie geoptimaliseerd wordt. Zowel bloeddruk als -flow worden als belangrijke determinanten van regionale weefselperfusie beschouwd. Dewelke van de twee het belangrijkst is, is minder goed geweten. Het blijft voorsnog dan ook de vraag of het optimaliseren van de flow dan wel de druk de beste strategie is om perfusietekort en eventuele bijhorende weefseleshade te voorkomen. Deze studie onderzoekt het effect van bloeddruk en -flowveranderingen op de cerebrale (ScO2) en globale zuurstofsaturatie (SvO2) tijdens cardiopulmonaire bypass, waarbij flow en druk op een gecontroleerde manier en onafhankelijk van elkaar kunnen veranderd worden.

Methode: Er werden 34 patienten geïncludeerd in de studie. Ieder van hen onderging een electieve cardiochirurgische ingreep met extracorporele circulatie. In elk van deze patiënten werd de respons onderzocht op veranderingen van bloeddruk, van bloedflow of van beiden. Er werden 4 verschillende hemodynamische toestanden gesimuleerd: een 20% daling van de flow, een 20% daling van de flow met herstel van bloeddruk dmv phenylefrine, een 20% daling van de bloeddruk dmv sodiumnitroprusside (SNP) onder baseline flow en een verhoogde flow met baseline bloeddruk. Elke hemodynamische toestand werd aangehouden voor een periode van 5 minuten. De volgorde van veranderingen in bloeddruk of -flow hing af van randomisatie door de computer.
Bij elke hemodynamische toestand werd het effect op de cerebrale en systeemveneuze saturatie geëvalueerd, alsook het effect op de systemische oxygen extraction ratio (OER).

Resultaten: Een daling van de flow bracht een daling van de ScO2 met zich mee [van 63,5 (7,4) tot 62,0 (8,5) %, p<0,001]. Wanneer de bloeddruk werd hersteld dmv phenylefrine tijdens de lage flow-status daalde de ScO2 verder van 61,0 (9,7) tot 59,2 (10,2) %, p<0,001. Toename van de flow bracht een toename van de ScO2 met zich mee van 62,6 (7,7) tot 63,6 (8,9) %, p=0,03, terwijl een daling van de bloeddruk met SNP geen effect had op de ScO2. De SvO2 en de OER waren beduidend lager bij een lage flow.

Conclusie: In de onderzochte populatie was er duidelijk een grotere invloed van flowveranderingen op de cerebrale en globale veneuze saturatie dan veranderingen van
arteriële bloeddruk. ScO₂ en SvO₂ waren beduidend lager en OER beduidend hoger bij een lage flow, onafhankelijk van de bloeddruk. Een stijging van de bloeddruk aan de hand van phenylefrinetoediening was geassocieerd met een daling van de cerebrale en systeemveneuze saturatie. Gezien de veranderingen in ScO₂ telkens gepaard gingen met veranderingen in SvO₂ en OER, kunnen we er van uitgaan dat er een correlatie bestaat tussen enerzijds de cerebrale saturatie en anderzijds de globale weefselperfusie en zuurstofbalans.

**Bewijs van publicatie:**