

## Effects of phenylephrine on the sublingual microcirculation during cardiopulmonary bypass

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**Background.** The objective of the present study was to investigate sublingual microvascular blood flow and microcirculatory haemoglobin oxygen saturation ( $S_{mcO_2}$ ) during cardiopulmonary bypass (CPB) using constant systemic blood flow but different perfusion pressures achieved by phenylephrine administration.

**Methods.** Fifteen patients undergoing coronary artery bypass grafting were enrolled in this pilot study. Systemic haemodynamics, oxygen transport variables, arterial and mixed venous blood gas analysis, and microcirculatory variables were determined after initiation of general anaesthesia, during CPB (systemic blood flow = 2.4 litre  $m^{-2}$ ), after increasing perfusion pressure by 20 mm Hg with a continuous infusion of phenylephrine, and after termination of phenylephrine infusion.

**Results.** CPB immediately resulted in a significant ( $P < 0.05$ ) decrease in systemic oxygen transport without alterations in sublingual microcirculatory blood flow and  $S_{mcO_2}$ . Increasing perfusion pressure from 47 (SD 9) to 68 (7) mm Hg using phenylephrine = 1.4 (1.0)  $\mu g kg^{-1} min^{-1}$  resulted in a significant decrease in sublingual small vessel blood flow (from median 2.5 to 1.8 arbitrary units) representing mostly capillary blood flow, but not in medium-sized vessels (median 3 to 2.8 arbitrary units). Concurrently, global tissue blood flow from 110 (54) to 197 (100) perfusion units and  $S_{mcO_2}$  increased from 72 (11)% to 84 (7)%, suggesting significant microcirculatory blood flow shunting in vessels with diameters  $> 25 \mu m$ .

**Conclusions.** Our data demonstrate that an increased perfusion pressure produced by phenylephrine at constant CPB flow may decrease microcirculatory blood flow in the sublingual mucosal microcirculation due to microvascular blood flow shunting.

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The four pillars in managing systemic oxygen delivery in patients on cardiopulmonary bypass (CPB) are controlling temperature, haematocrit, systemic blood flow, and the arterial perfusion pressure.<sup>1</sup> Arterial perfusion pressure during CPB is as important as arterial pressure under non-bypass conditions. Even during mild hypothermia, pressure-flow autoregulation remains active.<sup>1-3</sup> Patients who were maintained at a mean arterial pressure (MAP) of 80 mm Hg during CPB had significantly less morbidity

and mortality than those managed at usual MAP of 50–60 mm Hg, suggesting that maintaining MAP during CPB at levels close to the patient's own autoregulatory range prevents hypoperfusion-related ischaemia and, thereby improves the outcome.<sup>4-6</sup>

Systemic arterial pressure during CPB can be influenced by changing pump flow or administering vasoactive agents.<sup>7</sup> However, the use of vasoconstrictor agents may provoke tissue hypoperfusion, despite restoration of

perfusion pressure.<sup>8,9</sup> Changes in microvascular perfusion alter oxygen supply to the tissue and may contribute to organ dysfunction in cardiac surgery patients on CPB.<sup>10</sup>

Data on whether the initiation of CPB influences the microvasculature and consequently tissue oxygenation are sparse and little is known about alterations in the microcirculation due to different perfusion pressures. We investigated the effects of a pressure increase produced using the selective  $\alpha_1$ -agonist phenylephrine during CPB with constant blood flow on the sublingual microcirculation. Sublingual microcirculatory variables were assessed with sidestream dark-field (SDF) imaging, laser Doppler velocimetry, and tissue reflectance spectrophotometry before and during CPB with different perfusion pressures but constant systemic blood flow. The sublingual mucosal microcirculation was chosen because of its easy accessibility and the well-described vulnerability to systemic haemodynamic deterioration.<sup>11</sup>

The primary goal of the present study was to determine changes in the sublingual microcirculation produced by increased perfusion pressure induced by phenylephrine during constant blood flow during CPB. The second aim was to observe changes in the sublingual microcirculation induced by the CPB itself.

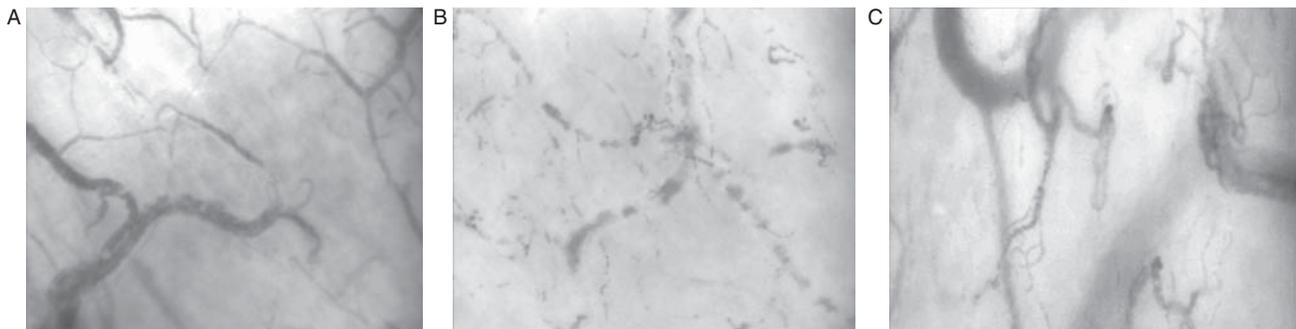
## Methods

The study protocol was approved by the ethical committee of the Innsbruck Medical University. Written informed consent was obtained from all patients the day before surgery. Fifteen patients undergoing elective coronary artery bypass grafting with CPB were included in the study. Exclusion criteria were diabetes mellitus, preoperative cerebral infarction or carotid artery disease, renal insufficiency, emergency surgery, cardiogenic shock defined as cardiac index (CI)  $<2.0$  litre  $\text{min}^{-1} \text{m}^{-2}$  and a pulmonary capillary wedge pressure (PCWP)  $>18$  mm Hg, and the need for vasopressor- or inotropic therapy before surgery.

Patient characteristics, including age, sex, body surface area, preoperative co-morbidities, preoperative medication,

and surgical diagnosis, were obtained from all patients. Premedication was with oral midazolam (3.75–7.5 mg) and anaesthesia was induced with fentanyl 0.5 mg irrespective of patient's body weight and midazolam 5–15 mg with rocuronium 0.9 mg  $\text{kg}^{-1}$  given for skeletal muscle relaxation. Patients were intubated and the lungs were mechanically ventilated with an oxygen/air mixture to achieve a  $P_{a_{O_2}} >20$  kPa and a  $P_{a_{CO_2}}$  level of 4.7–6.0 kPa. Anaesthesia was maintained with an i.v. infusion of remifentanyl 2 mg  $\text{h}^{-1}$  irrespective of patient's body weight and inhalation of sevoflurane with an end-tidal concentration of 1.0%. After induction of anaesthesia, a pulmonary artery catheter was inserted (Edwards Lifesciences, Irvine, CA, USA). Cardiac output measurements were made in triplicate with ice-cold boluses of 10 ml saline. Intraoperative fluid therapy was administered guided by transoesophageal echocardiography and pulmonary artery catheter measurements to achieve normovolaemia. Patients requiring vasopressor support, inotropic therapy, or both after induction of anaesthesia were excluded from the present study.

Before initiation of CPB, heart rate, MAP, central venous pressure, CI, stroke volume index, mean pulmonary artery pressure, PCWP, arterial and mixed-venous acid–base status, and blood oxygen tensions were determined. Systemic oxygen delivery index was calculated by multiplying systemic blood flow with arterial oxygen content. For systemic oxygen uptake index determination, systemic blood flow was multiplied with the arteriovenous oxygen content difference. Systemic blood flow was determined pre-CPB with a pulmonary artery catheter, on bypass with a flowmeter connected on the heart lung machine (Stöckert S5, Stöckert, Munich, Germany). Sublingual microcirculatory flow index (MFI) for small (10–25  $\mu\text{m}$ , representing predominantly capillaries) and medium vessels (between 26 and 50  $\mu\text{m}$  including mostly post-capillary venules) was assessed with SDF imaging (MicroScan<sup>TM</sup>, MicroVision Medical, Amsterdam, The Netherlands) (Fig. 1). In addition, sublingual microvascular blood flow was measured with a laser Doppler flowmeter (LDF) (O2C<sup>TM</sup>, LEA Medizintechnik, Giessen,



**Fig 1** Visualization of the microcirculation in the sublingual mucosal area recorded with the SDF imaging technique. (A) After initiation of CPB without haemodynamic intervention; (B) during pressure increase with phenylephrine; and (C) after discontinuation of phenylephrine. Note the diminished functional capillary density in a patient on CPB with pressure increase with phenylephrine.

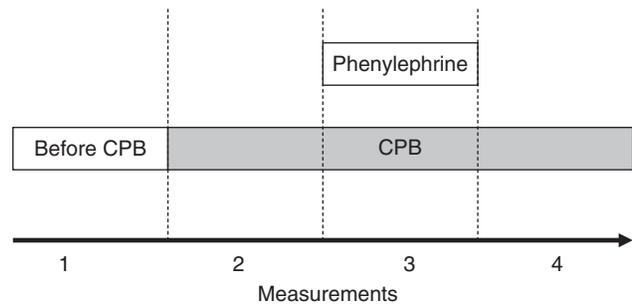
Germany), and microcirculatory haemoglobin oxygen saturation ( $S_{mc_{O_2}}$ ) was investigated with a tissue reflectance spectrophotometer (TRS) (O2C™, LEA Medizintechnik).

SDF imaging uses a non-invasive intravital microscope developed for assessment of the human microcirculation without using fluorescent dyes in clinical practice.<sup>12</sup> With the SDF device, microcirculatory blood flow can be qualitatively assessed with differentiation in continuous, sluggish, stop and go, or no flow patterns. The instrument consists of a small endoscopic-like light guide attached to a light source with filters. The examined tissue is illuminated with light with a wavelength of 530 nm permitting optimal imaging of the microcirculation, because of identical light absorption of oxy- and deoxyhaemoglobin at this wavelength. Within the tissue, light is scattered, depolarized, and reflected. Since the emitted light is primarily absorbed by haemoglobin, red cells can be remarkably well observed in all vessels. The illuminated light and reflected light travel via independent pathways. A 5 times magnifying lens is used to project the image onto a video camera. Two sequences of 15 s duration (30 s) at each time point were digitally recorded on a personal computer. The video files are evaluated offline with a software program (MAS Analysis Software Version 2.1, MicroVision Medical) in a blinded fashion. The MFI is a semi-quantitative method to describe microvascular flow quality from the recorded movie. A picture of the video is divided into four quadrants with examples of vessel classifications: small (10–25  $\mu\text{m}$ ) and medium (26–50  $\mu\text{m}$ ). Both small and medium vessels in each quadrant are described as no flow with 0 scoring points, intermittent flow (1 point), sluggish flow (2 points), and continuous flow (3 points). The points of all four quadrants are summed and divided by four to give the MFI.<sup>13</sup>

The LDF is a non-invasive instrument permitting real-time measurement of microvascular perfusion, particularly in the skin.<sup>12</sup>

The TRS was originally introduced by Sato and colleagues<sup>14</sup> and advanced by Frank and colleagues<sup>15</sup> as a non-invasive method for assessing microcirculatory haemoglobin oxygen saturation ( $S_{mc_{O_2}}$ ) and changes in tissue haemoglobin concentration.<sup>12</sup> Absolute values of  $S_{mc_{O_2}}$  are calculated using an algorithm, originally developed by Dümmler and described in detail by Frank and colleagues.<sup>15</sup> LDF- and TRS-derived variables were recorded for a period of at least 100 s. In contrast to the SDF device, we tried to keep the LDF/TRS device in the same position during the whole study period. Mean values of these variables were used for statistical comparison.

Before aortic cannulation, heparin 300  $\text{u kg}^{-1}$  was administered i.v. and supplemented as required to achieve an activated coagulation time of  $>400$  s. The perfusion system consisted of a hollow fibre membrane oxygenator (Marquette Medic Systems, Milwaukee, WI, USA), a hard shell venous reservoir, and roller pumps (Stöckert, Munich, Germany). The extracorporeal circuit



**Fig 2** Schematic diagram of the study. Data were collected after initiation of anaesthesia before starting CPB (measurement time point 1), after initiation of CPB without haemodynamic intervention (time point 2), during pressure increase with phenylephrine (time point 3), and after discontinuation of phenylephrine during extracorporeal circulation (time point 4).

was primed with 1000 ml lactated Ringer's solution, 250 ml mannitol 150  $\text{mg litre}^{-1}$ , and 500 ml gelatine. Cardioprotection was achieved with intermittent St Thomas II cardioplegic solution (Fresenius Kabi, Graz, Austria). Target systemic blood flow using non-pulsatile CPB was 2.4  $\text{litre min}^{-1} \text{m}^{-2}$  throughout the study period. The target temperature was 32–33°C, continuously measured by a thermistor in the urinary bladder. During CPB,  $P_{a_{O_2}}$  was maintained  $>20$  kPa and  $P_{a_{CO_2}}$  between 4.7 and 6.0 kPa. All measurements on CPB were made after aortic cross-clamping. The trigger haematocrit for blood transfusion was set at 20%; no blood had to be given during the study period.

At a body temperature of  $<34^\circ\text{C}$ , a haematocrit of  $>20\%$ , and a CPB flow rate index of 2.4  $\text{litre min}^{-1} \text{m}^{-2}$ , perfusion pressure, arterial and mixed venous acid–base status and blood oxygen tension, systemic oxygen transport variables, and sublingual microcirculatory variables were determined (Fig. 2). Approximately 10 min after the first measurement on CPB, the perfusion pressure was increased by 20 mm Hg from the first measurement on CPB with a continuous i.v. infusion of phenylephrine. After achieving the target perfusion pressure and a stabilization period of about 10 min, a second measurement on CPB was performed without any manipulation on systemic blood flow. The phenylephrine infusion was stopped, and after the perfusion pressure had decreased and after additional stabilization time of about 10 min, the last measurement was performed.

#### Data analysis and statistics

This study was planned as a pilot study. Therefore, no sample size estimation has been made. A Kolmogorov–Smirnov test was performed for analysing normality distribution. The assumption of normality was fulfilled in the measurements and data are presented as mean (SD). An analysis of variance for repeated measurements was performed to analyse differences in means within patients.

**Table 1** Characteristics and premedication of 15 patients undergoing elective coronary artery bypass grafting included in the study. Continuous data are mean (SD) except for age which is given as median (range). BSA, body surface area; CABG, number of coronary artery bypass grafts

Characteristic	Mean (SD)
Age (yr)	67 (53–81)
Weight (kg)	79.6 (12)
Height (cm)	169.4 (7.9)
BSA	1.9 (0.2)
CABG median (range)	3 (2–4)
Sex	
Female	5/15 (33.3%)
Male	10/15 (66.6%)
Drugs	
β-Blockers	7/15 (46.7%)
ACE-inhibitors	8/15 (53.3%)
Calcium antagonists	1/15 (6.7%)
Nitro compounds	5/15 (33.3%)
Aspirin/clopidogrel	8/15 (53.3%)
Statins	10/15 (66.6%)

Global hypothesis was tested two-sided with a 0.05 significance level. In the case of significant differences, further comparisons were made with either Student’s paired *t*-tests or the Wilcoxon test to compare systemic and microcirculatory variables, as appropriate. A software program was used for data analysis (SYSTAT, Systat Software Inc., Richmond, CA, USA). Because four comparisons were performed in a repeated measures design, the significance level was set to a Bonferroni adjusted *P*-value of 0.0125. All data are given as mean values (SD), if not indicated otherwise.

**Table 2** Systemic and microvascular variables. Variables were recorded in each patient after initiation of general anaesthesia, during CPB (systemic blood flow=2.4 litre m<sup>-2</sup>), after increasing perfusion pressure by 20 mm Hg due to continuous infusion of phenylephrine, and after termination of phenylephrine infusion. CPB, cardiopulmonary bypass; Hb, haemoglobin; Hct, haematocrit; pHa, arterial pH; HCO<sub>3</sub><sup>-</sup>, arterial bicarbonate; arterial BE, base excess; Pa<sub>o2</sub>, arterial oxygen tension; Pa<sub>co2</sub>, arterial carbon dioxide tension; Sv<sub>o2</sub>, mixed central venous oxygen saturation; DO<sub>2</sub>I, systemic oxygen delivery index; VO<sub>2</sub>I, systemic oxygen uptake index; PU, microvascular perfusion units; Smc<sub>o2</sub>, microcirculatory haemoglobin oxygen saturation; MFI<sub>s</sub>, small vessel microvascular flow index; MFI<sub>m</sub>, medium vessel microvascular flow index. Data are given as mean (SD). MFI<sub>s</sub> and MFI<sub>m</sub> are given as median and inter-quartile range in brackets. \*Significant (*P*<0.0125) compared between *before CPB* and *CPB (before phenylephrine)*. †Significant (*P*<0.0125) compared between *before phenylephrine* and *phenylephrine*. ‡Significant (*P*<0.0125) compared between *after phenylephrine* and *phenylephrine*

	Before CPB	CPB			<i>P</i> -value
		Before phenylephrine	Phenylephrine	After phenylephrine	
<b>Systemic variables</b>					
Perfusion pressure (mm Hg)	72.5 (10.8)	47.0 (8.8)*	68.1 (7.0) <sup>†,‡</sup>	48.7 (6.0)	<0.001
Syst. flow index (litre m <sup>-2</sup> )	2.6 (0.4)	2.4 (0.0)*	2.4 (0.0)	2.4 (0.0)	<0.001
Temperature (°C)	35.8 (0.4)	33.2 (1.2)*	32.3 (1.4)	32.8 (1.3)	<0.001
Hb (g dl <sup>-1</sup> )	12.1 (1.3)	7.9 (1.1)*	8.2 (0.8)	8.2 (0.7)	<0.001
Hct (%)	35.5 (3.7)	23.3 (3.1)*	24.0 (2.5)	24.3 (2.1)	<0.001
pHa	7.41 (0.04)	7.35 (0.04)*	7.36 (0.04)	7.35 (0.05)	<0.001
HCO <sub>3</sub> <sup>-</sup> (mmol litre <sup>-1</sup> )	24.6 (2.2)	22.7 (2.2)	23.2 (2.2)	23.0 (2.2)	<0.001
BE	0.0 (2.2)	-2.7 (2.5)	-2.2 (2.6)	-2.6 (2.7)	<0.001
Pa <sub>o2</sub> (kPa)	33.3 (16.0)	36.3 (6.0)	30.3 (3.5)	30.6 (5.7)	0.243
Pa <sub>co2</sub> (kPa)	5.2 (0.8)	5.6 (0.5)	5.5 (0.4)	5.5 (0.5)	0.196
Sv <sub>o2</sub> (%)	84.2 (2.4)	78.9 (3.8)*	79.3 (4.9)	79.3 (5.1)	0.002
DO <sub>2</sub> I (ml m <sup>-2</sup> min <sup>-1</sup> )	457 (97)	279 (33)*	282 (26)	283 (22)	<0.001
VO <sub>2</sub> I (ml m <sup>-2</sup> min <sup>-1</sup> )	98 (52)	71 (12)	68 (12)	65 (15)	0.006
<b>Microvascular variables</b>					
PU (arbitrary units)	120 (105)	110 (54)	197 (100) <sup>†,‡</sup>	89 (66)	0.007
Smc <sub>o2</sub> (%)	73 (7)	72 (11)	84 (7) <sup>†,‡</sup>	72 (8)	<0.001
MFI <sub>s</sub> (arbitrary units)	2.1 (1.2)	2.5 (2)	1.8 (1.2) <sup>†</sup>	2.2 (1.2)	0.039
MFI <sub>m</sub> (arbitrary units)	3 (2)	3 (2)	2.8 (1)	2.9 (2)	0.281

## Results

Nineteen patients undergoing elective CABG surgery were enrolled in the study. Four patients were excluded from the study because of a baseline CI <2.0 litre min<sup>-1</sup> m<sup>-2</sup> (one patient) or the need for vasopressor therapy before CPB (three patients). Characteristics of the patients studied are presented in Table 1.

### Variables after initiation of CPB

Initiation of CPB resulted in a significant reduction in perfusion pressure (Table 2). The decrease in arterial haemoglobin concentration due to haemodilution led to a significant decrease in systemic oxygen delivery concomitant with an increase in systemic oxygen extraction ratio. A decrease of arterial pH could be observed in patients on CPB. No alterations in microcirculatory variables were observed after starting CPB (Table 2).

### Microcirculatory variables during CPB

Infusion of phenylephrine at a mean (SD) rate of 1.4 (1.0) µg kg<sup>-1</sup> min<sup>-1</sup> significantly increased perfusion pressure from 47 (9) to 68 (7) mm Hg without alterations in systemic oxygen transport variables or blood gas variables (Table 2). Phenylephrine resulted in a significant decrease in the MFI of the small vessels caused by a more sluggish microvascular flow pattern, including the so-called ‘stop and go’ phenomena of erythrocytes within capillaries. In contrast, the MFI remained constant in medium-sized

vessels after induction of high perfusion pressure (Table 2). Total quantitatively assessed microcirculatory blood flow with the laser Doppler device increased significantly after phenylephrine administration accompanied by an increase in  $\text{Smc}_{\text{O}_2}$ .

After termination of the phenylephrine infusion, microcirculatory blood flow abnormalities,  $\text{Smc}_{\text{O}_2}$ , and quantitatively assessed microcirculatory blood flow returned to pre-phenylephrine values (Table 2).

## Discussion

During CPB with constant flow, increasing perfusion using the selective  $\alpha_1$ -adrenoreceptor agonist phenylephrine resulted in a decrease of sublingual small vessel microcirculatory blood flow, elevated microcirculatory haemoglobin oxygen saturation, and quantitatively assessed total microcirculatory blood flow.

### *Variables after initiation of CPB*

The use of priming solution in the extracorporeal circuit caused a decrease in haematocrit after initiation of CPB. The decrease in arterial oxygen content decreased systemic oxygen delivery. No alterations of sublingually assessed microcirculatory variables could be observed. Neither qualitatively nor quantitatively assessed microcirculatory blood flow showed significant differences compared with measurements before CPB. In addition,  $\text{Smc}_{\text{O}_2}$  did not change after beginning bypass, despite an increased systemic oxygen extraction in order to maintain an insignificant reduction of systemic oxygen uptake by mean of 25%. Since tissue spectrophotometry measures  $\text{Smc}_{\text{O}_2}$  mainly in post-capillary venules, where about 85% of the microcirculatory blood volume is present,<sup>16 17</sup> one might have expected that increased systemic oxygen extraction is mirrored by a decrease in intravascular haemoglobin oxygen saturation.

Our observation regarding unchanged microcirculatory variables is consistent with a report demonstrating preserved perfusion of superficial and deep layers in the renal cortex in pigs after starting and during CPB.<sup>18</sup> In humans, Bauer and colleagues<sup>19</sup> found a slightly decreased functional capillary density after starting CPB. Differences in systemic blood flow and temperature might explain the small differences between the study by Bauer and colleagues and the present investigation. Wagner and colleagues<sup>20</sup> observed significantly reduced capillary density and decreased arteriolar diameters shortly after initiation of CPB in s.c. tissue of newborn piglets. Haisjackl and colleagues<sup>21</sup> demonstrated that CPB is associated with diminished oxygenation of intestinal mucosa caused by regional redistribution. These heterogeneous and conflicting results regarding the effects of CPB on microcirculatory blood flow may point at significant differences in microcirculatory blood flow regulation during CPB in

different organs and tissues. Heterogeneity in vessel receptor types, receptor density, and the importance of local blood flow autoregulation, which principally reflects the strength of the metabolic component of microcirculatory regulation in the tissue,<sup>1</sup> may explain the variability of microcirculatory blood flow and oxygen supply to different organ beds. This heterogeneity in microcirculatory blood flow may also be explained by an organ-specific hierarchy of organ blood flow during CPB,<sup>22 23</sup> and may explain many of the problems regarding the correct clinical interpretation of data obtained from microcirculatory monitoring at one specific origin.<sup>12</sup>

Also changes of systemic variables have significant effects on peripheral microcirculatory function. A high arterial  $P_{\text{O}_2}$  level due to higher oxygen concentration when starting the CPB may also influence the  $\text{Smc}_{\text{O}_2}$ . Furthermore, since it is known that microcirculatory haematocrit is lower than the systemic one, one may not necessarily expect a change in microcirculatory blood flow.

In the present study, blood flow and oxygen supply to sublingual tissue was maintained after initiation of CPB. Therefore, increased systemic oxygen extraction results from reduced systemic oxygen delivery to other tissues. The discrepancy between the microcirculatory behaviour of sublingual tissue and systemic oxygen extraction points to the possibility of major differences in the regulation of regional oxygen delivery to tissue during CPB as mentioned above.

### *Microcirculatory variables during CPB*

Infusion of the pure  $\alpha_1$ -adrenoreceptor agonist phenylephrine during CPB significantly increased perfusion pressure during constant systemic blood flow by increasing systemic vascular resistance without alterations in systemic oxygen transport variables or acid-base status. In spite of unchanged systemic parameters, activation of sympathetic  $\alpha_1$ -adrenergic receptors resulted in an impairment of sublingual microcirculatory tissue oxygen supply due to a deterioration in small vessel blood flow primarily including capillary vessels. This was accompanied by a significant decrease in capillary blood flow quality during phenylephrine infusion. A largely continuous capillary blood flow passed into a more sluggish flow pattern with a substantial number of capillaries displaying 'stop and go' phenomena.

Interestingly,  $\text{Smc}_{\text{O}_2}$  and total microcirculatory blood flow increased during phenylephrine infusion. Since tissue spectrophotometry measures  $\text{Smc}_{\text{O}_2}$  mainly in post-capillary venules, where about 85% of the microcirculatory blood volume is present as mentioned above, we assume a reduced oxygen uptake in the sublingual tissues.

The discrepancy between quantitatively assessed sublingual blood flow measured with laser Doppler and semi-quantitatively analysis of microcirculatory blood flow using SDF imaging most probably represents a

combination of two factors: first, LDF measurements do not distinguish between arterioles, capillaries, or venules, but generate a signal from number of red blood cells flowing within the penetration depth and area of the laser multiplied by the mean velocity of these cells, independently of the flow quality within defined anatomic vessels.<sup>12</sup> In addition, substantial differences in tissue penetration exist between the methods used. Although SDF imaging is limited to visible vessels located just beneath the tongue mucosa, LDF measurements include vessels located much deeper in the tissue. In one set of experiments investigating tissue oxygen supply to the jejunal mucosa in pigs, we were able to demonstrate that the laser light of the LDF and even the visible light of a tissue spectrophotometer was able to penetrate at least the whole jejunal wall, representing a distance of  $\sim 2$  mm.<sup>24</sup> Penetration to deeper tissues may reflect other flow behaviour, for example, microvascular blood flow in the skeletal muscle bed.<sup>25 26</sup> Secondly, infusion of phenylephrine may have induced microcirculatory shunting away from the capillary bed. Microcirculatory blood flow shunting may be of 'functional' origin implying a redistribution of capillary blood flow away from longer 'nutrient' capillaries to very short capillaries with critically decreased red cell transit times representing functional microcirculatory shunt. Unfortunately, we were not able to observe this phenomenon directly in sublingual vessels under investigation using SDF imaging. The opening of true anatomical arteriovenous shunts in the tongue with short circuiting of microvascular blood flow may be another explanation. The existence of arteriovenous anastomoses in the tongue was demonstrated by Saxena and Verdouw.<sup>27</sup> They could show the presence of a shunt phenomenon with the use of 25 and 35  $\mu\text{m}$  microspheres in anaesthetized pigs.

With the methods used in this study, we are not able to definitively answer the question where short circuiting of microvascular blood flow occurs. However, the discrepancy between total tongue microcirculatory blood flow changes, the increase of  $\text{Smc}_{\text{O}_2}$  indicating a decreased tissue oxygen uptake occurring simultaneously with a reduction in small vessel microvascular blood flow, suggests the occurrence of arteriovenous blood short circuiting during phenylephrine infusion.

Little is described in the literature regarding regional oxygen supply and uptake alterations after vasopressor application. Le and colleagues<sup>28</sup> demonstrated a progressive increase in the coronary sinus  $\text{PO}_2$  by increasing coronary perfusion pressure with phenylephrine in dogs. They observed the presence of coronary arteriovenous shunting due to an increase in coronary driving pressure. In endotoxic mice, Albuszies and colleagues<sup>29</sup> demonstrated an increase in hepatic microcirculatory haemoglobin oxygen saturation after norepinephrine infusion to maintain normotension. Nevertheless, the authors did not associate this observation with a possible shunting of oxygen at the microcirculatory level.

The lack of systemic alterations during CPB due to vasoconstrictor administration may be explained from the heterogeneity of microcirculatory blood flow and oxygen supply in different organ beds. From the present data, we conclude that the use of phenylephrine for perfusion pressure increase should be critically deliberated during hypothermic CPB. Administering phenylephrine may mask hypoperfusion at the capillary levels in some organs, despite restoration of perfusion pressure.<sup>8</sup>

Pressure management with phenylephrine during CPB may be harmful to tissues or even organs, especially in those with a pre-existing obstruction or stenosis in delivering arterioles. In our present study, systemic oxygen uptake remained constant during the bypass period. On the other hand, we can conclude from  $\text{Smc}_{\text{O}_2}$  values that sublingual tissue oxygen uptake decreased after pressure increase, and returned to pre-phenylephrine values after discontinuation of phenylephrine administration. This decrease in oxygen uptake is an organ or tissue-specific effect, not observed in the systemic oxygen uptake calculation, and independently of the temperature. The reduction of systemic oxygen uptake is adaptive after initiation of CPB due to hypothermia. But, this locally seen effect of oxygen uptake reduction is independent of hypothermia, because it occurs solely due to administration of phenylephrine besides constant conditions.

We cannot exclude some background changes over time in our present study. But, we observed that all microcirculatory variables returned to pre-phenylephrine values after discontinuation of the vasopressor. Furthermore, all acid-base variables, haematocrit, and systemic oxygen transport variables did not differ during CPB in all three measurements. For that reason, we believe that the background changes over the time are minimal and do not significantly alter our results.

In conclusion, initiation of CPB resulted in no alterations in sublingual microcirculation, despite a reduction in systemic oxygen delivery. Other organ beds with different blood flow hierarchy during extracorporeal circulation may be responsible for the observed increased systemic oxygen extraction ratio than the sublingual microvasculature. A pressure increase with the pure  $\alpha_1$ -adrenoceptor agonist phenylephrine during CPB and constant blood flow did not alter systemic oxygen transport variables, but resulted in an impairment of microcirculatory blood flow quality leading to deterioration in microvascular flow pattern of erythrocytes within capillaries resulting in a significant reduction of small vessel microvascular blood flow. This observation was accompanied with decreased oxygen uptake in the sublingual tissue. This phenomenon may be explained by the occurrence of arteriovenous blood short circuiting during phenylephrine infusion. Increasing systemic arterial pressure with an  $\alpha_1$ -adrenoceptor agonist may mask possible tissue hypoperfusion on the sublingual microcirculatory level, despite sufficient systemic arterial pressure.

## Funding

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