The microcirculatory response during cardiac surgery
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Distinct alterations in sublingual microcirculatory blood flow and hemoglobin oxygenation in on-pump and off-pump coronary artery bypass graft surgery

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Abstract

Objective: The authors hypothesized that cardiopulmonary bypass (on-pump) is associated with more severe changes in the microcirculatory blood flow and tissue oxygenation as compared with off-pump coronary bypass surgery.

Design: An observational study.

Setting: A university hospital and teaching hospital.

Participants: Patients undergoing on-pump (n = 24) or off-pump (n = 24) cardiac surgery.

Interventions: Microcirculatory measurements were performed before pump and 10 minutes after the switch to pump or before and during cardiac luxation in off-pump patients.

Measurements and Main Results: Sublingual microcirculatory perfusion was investigated using side-stream dark field imaging, and sublingual microcirculatory oxygenation was measured using reflectance spectrophotometry. Conversion to pump-flow resulted in an increase in cardiac output from $4.0 \pm 0.2$ to $4.8 \pm 0.3$ L/min ($p < 0.01$) and a 40% reduction in arterial hemoglobin concentration. Cardiopulmonary bypass was associated with an increase in venular blood velocity from $349 \pm 201$ µm/s to $563 \pm 227$ µm/s ($p < 0.05$), a reduction in functional capillary density of 43%, and an increase in hemoglobin oxygenation of the red blood cells in the remaining filled capillaries from $47.2\% \pm 6.1\%$ to $59.7\% \pm 5.2\%$ ($p < 0.001$). The decrease in cardiac output during cardiac luxation from $4.5 \pm 1.7$ to $1.8 \pm 0.8$ L/min ($p < 0.01$) without hemoglobin changes was associated with a complete halt of capillary blood flow and a reduction in maximum capillary blood velocity from $895 \pm 209$ to $396 \pm 178$ _m/s ($p < 0.01$). The functional capillary density remained unchanged, whereas the hemoglobin oxygenation declined from $64.2\% \pm 9.1\%$ to $48.6\% \pm 8.7\%$ ($p < 0.01$).

Conclusions: On-pump and off-pump cardiac surgery is associated with distinct alterations in sublingual microcirculatory perfusion and hemoglobin oxygenation. Although on-pump surgery results in a fall out of capillaries resulting in a decreased oxygen extraction, off-pump surgery results in a cessation of flow during luxation resulting in decreased convection of oxygen transport.

Keywords: sublingual microcirculation, cardiopulmonary bypass, intravital microscopy, reflectance spectrophotometry
Distinct alterations in sublingual microcirculation in on-pump and off-pump CABG

Introduction

Both on-pump and off-pump coronary artery bypass graft (CABG) surgical procedures are associated with specific hemodynamic alterations, leading to distinct effects on microcirculatory blood flow and tissue oxygenation. Indeed, it has been shown that both types of cardiac surgery are associated with a reduction in sublingual microcirculatory hemodynamic alterations including microvascular blood flow and functional capillary density.\textsuperscript{1,3} Interestingly, it has been shown that microcirculatory deterioration is less prominent in off-pump cardiac surgery as comparison to on-pump surgery patients.\textsuperscript{3} Because alterations in microcirculatory perfusion may be associated with morbidity and mortality, more insight in the role of microcirculatory flow during hemodynamic alterations in cardiac surgical procedures is needed.\textsuperscript{4,5}

Although clinical studies present visual information about the sublingual microcirculatory blood flow, functional information about the association between microcirculatory blood flow alterations and local tissue oxygenation is mostly limited to animal studies.\textsuperscript{6} During fluid resuscitation in an animal model for acute hemorrhagic shock, sublingual microcirculatory parameters including microvascular blood flow and microcirculatory hemoglobin oxygen saturation were investigated using microlaser Doppler velocimetry and tissue reflectance spectrophotometry, respectively.\textsuperscript{7} Furthermore, side-stream darkfield (SDF) imaging was performed to visualize the sublingual microcirculation and to evaluate the flow quality in this animal study.\textsuperscript{7} However, there are only limited data concerning simultaneous measurements of microcirculatory blood flow and hemoglobin oxygen saturation in human subjects.

The authors previously quantified the behavior of sublingual microcirculatory perfusion and oxygenation in patients during nitroglycerin-induced hypotension using side-stream darkfield imaging in combination with reflectance spectrophotometry analysis and microlaser Doppler measurements.\textsuperscript{8} Using these techniques, the authors assessed the function of the sublingual microcirculation during on-pump and off-pump CABG surgery in combination with measurements of microcirculatory oxygenation and perfusion. In particular, the study focuses on changes in microcirculatory blood flow and tissue oxygenation at the initiation of cardiopulmonary bypass during on-pump surgery and during cardiac positioning in off-pump surgery. The authors hypothesized that cardiopulmonary bypass is associated with more severe changes in the microcirculatory blood flow and tissue oxygenation as compared with off-pump surgery.
Materials and methods

The study was approved by the Human Subjects Committees of the Academic Medical Center and Onze Lieve Vrouwe Gasthuis (Amsterdam, the Netherlands), and written informed consent was obtained from all patients. The study population consisted of 24 patients undergoing elective on-pump CABG surgery and 24 patients undergoing elective off-pump CABG surgery. Exclusion criteria were an ejection fraction less than 0.40, advanced chronic lung disease, redo operations, pregnancy, infection, and vasculitis. In on-pump and off-pump groups, sublingual microcirculatory perfusion was investigated using SDF imaging (n = 12 per group), whereas sublingual microcirculatory oxygenation was measured using reflectance spectrophotometry (RS, n = 12 per group). Optical interference between both techniques prohibit simultaneous SDF and RS measurements in the same patient.

Systemic hemodynamic monitoring included continuous invasive arterial blood pressure and cardiac output measurements using a pulmonary artery catheter in all patients. None of the patients were monitored by transesophageal echocardiography. Hemoglobin concentrations were determined before and at 10 minutes after the switch to cardiopulmonary bypass in on-pump patients and before and after cardiac positioning in off-pump patients. The microcirculatory measurements were performed under the lowest MAP observed during cardiac positioning.

Temperature was continuously monitored in both on-pump and off-pump groups using a rectal temperature probe. Additional heating consisted of a warming mattress that was used in both groups. In the on-pump group, anesthetic induction and maintenance was performed with propofol (Diprivan; Astra Zenica, the Netherlands; 5-15 mL/h), fentanyl, and pancuronium (Pavulon; Organon, the Netherlands; 0.1 mg/kg). On-pump patients were cooled to 32 °C and oxygenated with a membrane oxygenator (COBE Cardiovascular Inc, CO). Hypotension after anesthetic induction and before the switch to cardiopulmonary bypass was treated by leg raising and volume resuscitation using 4% modified gelatin (Gelofusine; B Braun, the Netherlands). In the off-pump group, anesthetic induction consisted of the infusion of fentanyl and pancuronium and maintenance with a mixture of 50%/50% O2/NO2 and sevoflurane (Sevorane; Abbott Laboratories, the Netherlands). Off-pump patients were kept at 37 °C. Hypotension caused by cardiac positioning in off-pump patients was treated by leg elevation and volume resuscitation with 4% modified gelatin. All patients received antifibrinolytic agents.
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In the on-pump group, achievement of an activated coagulation time of greater than 400 seconds by full heparinization (3 mg/kg) was followed by connection of the extracorporeal circuit (Sarns 9000 Perfusion System; 3M Health Care Group, MI) through cannulation of the ascending aorta and the right atrium. The aortic cross-clamp was placed within 10 minutes after the onset of cardiopulmonary bypass, resulting in nonpulsatile blood flow fully generated by a roller pump. The flow rates were kept at 2.2 to 2.4 L/m^2/min. The oxygenator priming solution contained 1,100 mL of Ringer solution, 300 mL of albumin, 200 mL of mannitol, and 50 mL of sodium bicarbonate, yielding a total standard mix of 1,650 mL.

In the on-pump group, measurements were performed at the same sublingual location just before the switch to cardiopulmonary bypass and at 10 minutes after the onset of cardiopulmonary bypass. In the off-pump group, continuous microcirculatory measurements were performed at the same sublingual location before and during cardiac positioning, which was part of all off-pump procedures reported in this study. Imaging of the sublingual mucosal microcirculation was performed using SDF imaging, which is a noninvasive handheld video microscopy whose light guide is placed on organ surfaces for direct microscopic observation of the microcirculation.9 A 5x magnifying lens providing an observation field area of 1 mm^2 projected the image through a video camera inside the device. This technique enables clear images of the microvasculature with the possibility to observe single flowing red blood cells on a connected monitor with a final magnification of 350x. Microcirculatory images and movies were recorded on digital tapes for offline computer analysis.

Dedicated automated microvascular analysis software was used to quantify functional capillary density.11 This software package allows calculation of microvascular blood velocity using space-time diagrams.12 A space-time image displays in a single static image for a single vessel the location of all erythrocytes as a function of time. Consecutive space-time images show the location of same erythrocytes in consecutive video frames as they traverse through the vessel resulting in diagrams. The slope of this diagram represents the blood velocity (space/time = velocity).

An optical probe (O2C; Lea Medizintechnik, Giessen, Germany) containing reflectance spectrophotometry was used by placement on the sublingual tissue to measure microcirculatory hemoglobin oxygen saturation. After removal of saliva by gauze, the optical fiber probe was placed and fixed under the tongue for continuous measurement in 1
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sublingual location. The tissue was illuminated by a visible white light (500-630 nm), and the spectrum of reflected light was measured. Analysis of this spectrum provides the hemoglobin oxygen saturation of the available erythrocytes.\textsuperscript{13,14}

All values are expressed as mean ± standard deviation or median with interquartile range. The 2-sided paired Student $t$ test was used for comparison of the variables before and after switch to pump and before and during cardiac positioning in the same patient. The Mann-Whitney $U$ test was applied in case of nonparametric data analysis.

Results

Patient demographics including age, sex, body surface area, the number of comorbidities, and the number of grafts for on-pump and off-pump CABG are presented in Table 1 and were comparable among groups. Moreover, baseline values before cardiopulmonary bypass or cardiac positioning of cardiac output, blood pressure, hemoglobin, and temperature were similar between on-pump and off-pump CABG groups (Table 2).

Conversion to cardiopulmonary bypass (i.e., a switch from pulsatile to continuous flow) resulted in acute alterations in systemic hemodynamics. The average cardiac output increased by 40% from $4.0 \pm 0.2$ to $4.8 \pm 0.3$ L/min ($p < 0.01$), whereas the mean arterial pressure (MAP) dropped from $67 \pm 7$ to $50 \pm 7$ mmHg ($p < 0.01$). This was paralleled by a decrease in the hemoglobin concentration of 40% from $7.4 \pm 0.9$ to $4.5 \pm 0.5$ mmol/L ($p < 0.01$) and blood temperature from $36.5^\circ \pm 0.4^\circ$C to $32.8^\circ \pm 1.1^\circ$C ($p < 0.01$, Table 2, on-pump). Cardiac positioning in off-pump surgery caused a sudden drop of cardiac output from $4.5 \pm 1.7$ to $1.8 \pm 0.8$ L/min, whereas the MAP decreased from $68 \pm 12$ to $35 \pm 10$ mmHg ($p < 0.01$). In contrast to on-pump patients, there were no changes in the hemoglobin concentration or blood temperature during cardiac positioning (Table 2, off-pump).

Figure 1 represents a typical image of the sublingual microcirculation before cardiopulmonary bypass and after 10 minutes during cardiopulmonary bypass. The space-time diagram of a venule, which changed from a wavy into a linear pattern, confirms the transition from pulsatile to continuous flow during conversion to cardiopulmonary bypass. Further analysis of the diagrams revealed an increase of blood velocity in the venules from $349 \pm 201 \mu$m/s to $563 \pm 227 \mu$m/s ($p < 0.05$). Capillary velocity analysis was not performed in the off-pump group because of the limited hemoglobin contrast, which is required for space-time diagrams.
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The functional capillary density reduced by 43% from 12.6 ± 4.2 to 6.9 ± 2.6 mm/mm² (p < 0.01). Consistently, microvascular hemoglobin oxygen saturation (μHbO₂) increased by 22% from 47.2% ± 6.1% to 59.7% ± 5.2% (p < 0.001, Table 3).

Table 1. Patient demographics for on-pump and off-pump CABG groups.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>On-pump</th>
<th>Off-pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>SDF 12</td>
<td>RS 12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71 ± 7</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>6/6</td>
<td>5/7</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Grafts (median)</td>
<td>3 (2-5)</td>
<td>3 (2-4)</td>
</tr>
</tbody>
</table>

Data are represented as mean ± standard deviation or median with interquartile range. BSA; body surface area
SDF, sidestream darkfield imaging; RS, reflectance spectrophotometry.

Table 2. Hemodynamic alterations in on-pump and off-pump CABG surgery.

<table>
<thead>
<tr>
<th></th>
<th>On-pump</th>
<th>Off-pump</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pump</td>
<td>During pump</td>
</tr>
<tr>
<td></td>
<td>(T=0)</td>
<td>(T=10 min)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.0 ± 0.2</td>
<td>4.8 ± 0.3*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>67 ± 7</td>
<td>50 ± 6*</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>7.4 ± 0.9</td>
<td>4.5 ± 0.5*</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.5 ± 0.4</td>
<td>32.8 ± 1.1*</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation. MAP, mean arterial pressure.
*p < 0.05 versus baseline values in either on-pump or off-pump CABG groups.
Figure 1. Representative SDF images and space-time diagrams of microcirculatory changes in on-pump CABG surgery. Typical images of the sublingual microcirculation (A) before and (B) during cardiopulmonary bypass are shown. (C and D) A spacetime diagram of a venule in the sublingual microcirculation before and during cardiopulmonary bypass, respectively. The change from a wavy into a linear pattern confirmed the transition from pulsatile to continuous flow during conversion to cardiopulmonary bypass. A, arteriole; V, venule; C, capillary.

Figure 2 represents a typical image of the sublingual microcirculation before and during positioning and includes the space-time diagram of a capillary showing a deceleration of blood flow to a complete halt. The maximum blood velocity in the capillaries decreased from $895 \pm 209$ to $396 \pm 178 \mu m/s$ ($p < 0.01$) and in some capillaries to 0 velocity. In the venules, there was no significant change found in blood velocity ($751 \pm 239$ to $596 \pm 192 \mu m/s$, $p < 0.18$). Moreover, the functional capillary density did not change ($15.9 \pm 1.1$ vs $14.6 \pm 1.3$).
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Figure 1. Representative SDF images and space-time diagrams of microcirculatory changes in on-pump CABG surgery. Typical images of the sublingual microcirculation (A) before and (B) during cardiopulmonary bypass are shown. (C and D) A space-time diagram of a venule in the sublingual microcirculation before and during cardiopulmonary bypass, respectively. The change from a wavy into a linear pattern confirmed the transition from pulsatile to continuous flow during conversion to cardiopulmonary bypass. A, arteriole; V, venule; C, capillary.

Figure 2. Representative SDF images and space-time diagrams of microcirculatory changes in off-pump CABG surgery. Typical images of the sublingual microcirculation (A) before and (B) during cardiac positioning are shown. (C) A space-time diagram of a capillary in the sublingual microcirculation during cardiac positioning, indicating a deceleration of blood flow to a complete halt caused by cardiac output failure during cardiac positioning. A, arteriole; V, venule; C, capillary.

Figure 2. Representative SDF images and space-time diagrams of microcirculatory changes in off-pump CABG surgery. Typical images of the sublingual microcirculation (A) before and (B) during cardiac positioning are shown. (C) A space-time diagram of a capillary in the sublingual microcirculation during cardiac positioning, indicating a deceleration of blood flow to a complete halt caused by cardiac output failure during cardiac positioning. A, arteriole; V, venule; C, capillary.

mm/mm2, $p < 0.65$), whereas the $\mu$HbO$_2$ declined 25% from 64.2% ± 9.1% to 48.6% ± 8.7% ($p < 0.01$, Table 3).

Figure 3 represents a typical example of a continuous recording of sublingual hemoglobin oxygen saturation in on-pump and off-pump surgery. Cardiopulmonary bypass and cardiac positioning reveal a direct but opposing effect on the microcirculation. The switch to
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cardiopulmonary bypass in on-pump patients causes an immediate increase in the \( \mu \text{HbO}_2 \), whereas cardiac positioning in off-pump patients causes a rapid decrease in \( \mu \text{HbO}_2 \), which recovers after repositioning the heart.

Table 3. Microcirculatory changes in on-pump and off-pump CABG surgery.

<table>
<thead>
<tr>
<th></th>
<th>On-pump</th>
<th></th>
<th>Off-pump</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pump</td>
<td>During pump (T=10 min)</td>
<td>Before cardiac positioning</td>
<td>During cardiac positioning</td>
</tr>
<tr>
<td>FCD (mm/mm(^2))</td>
<td>12.6 ± 4.2</td>
<td>6.9 ± 2.6*</td>
<td>15.9 ± 4.1</td>
<td>14.6 ± 3.1</td>
</tr>
<tr>
<td>Velocity capillary (µm/s)</td>
<td>NA</td>
<td>NA</td>
<td>895 ± 209</td>
<td>396 ± 178*</td>
</tr>
<tr>
<td>Velocity venule (µm/s)</td>
<td>349 ± 201</td>
<td>563 ± 227*</td>
<td>751 ± 239</td>
<td>596 ± 192</td>
</tr>
<tr>
<td>( \mu \text{HbO}_2 ) (%)</td>
<td>47.2 ± 6.1</td>
<td>59.7 ± 5.2*</td>
<td>64.2 ± 9.1</td>
<td>48.6 ± 8.7*</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation. FCD, functional capillary density.

*\( p < 0.05 \) versus baseline values in either on-pump or off-pump CABG groups.
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Cardiopulmonary bypass

![chart showing %HbO2 over time during and after bypass]

Cardiac positioning

![chart showing %HbO2 over time during and after positioning]

**Figure 3.** Typical recordings of sublingual microcirculatory hemoglobin oxygen saturation in an on-pump and off-pump CABG patient. Cardiopulmonary bypass time and cardiac positioning time are indicated in the boxes in the upper and lower recording, respectively.
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REFERENCES


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