Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass

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Koning NJ, Simon LE, Asfar P, Baufreton C, Boer C. Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. Am J Physiol Heart Circ Physiol 307: H967–H975, 2014. First published July 25, 2014; doi:10.1152/ajpheart.00397.2014.—Previously we showed that cardiopulmonary bypass (CPB) during cardiac surgery is associated with reduced sublingual microcirculatory perfusion and oxygenation. It has been suggested that impaired microcirculatory perfusion may be paralleled by increased heterogeneity of flow in the microvascular bed, possibly leading to arteriovenous shunting. Here we investigated our hypothesis that acute hemodynamic disturbances during extracorporeal circulation indeed lead to microcirculatory heterogeneity with hyperdynamic capillary perfusion and reduced systemic oxygen extraction. In this single-center prospective observational study, patients undergoing cardiac surgery with (n = 18) or without (n = 13) CPB were included. Perioperative microcirculatory perfusion was assessed sublingually with sidestream darkfield imaging, and recordings were quantified for microcirculatory heterogeneity and hyperdynamic capillary perfusion. The relationship with hemodynamic and oxygenation parameters was analyzed. Microcirculatory heterogeneity index increased substantially after onset of CPB [0.5 (0.0–0.9) to 1.0 (0.3–1.3); P = 0.031] but not during off-pump surgery. Median capillary red blood cell (RBC) velocity increased intraoperatively in the CPB group only [1,600 (913–2,500 µm/s) vs. 380 (190–480 µm/s); P < 0.001], with 31% of capillaries supporting high RBC velocities (>2,000 µm/s). Hyperdynamic microcirculatory perfusion was associated with reduced arteriovenous oxygen difference and systemic oxygen consumption during and after CPB. The current study provides the first direct human evidence for a microvascular shunting phenomenon through hyperdynamic capillaries following acute physiological disturbances after onset of CPB. The hypothesis of impaired systemic oxygen offloading caused by hyperdynamic capillaries was supported by reduced blood arteriovenous oxygen difference and low systemic oxygen extraction associated with CPB.

blood flow velocity; cardiac surgical procedures; microcirculation; oxygen consumption

THE MICROCIRCULATION IS AN IMPORTANT END ORGAN IN THE PATHOPHYSIOLOGY OF CRITICAL ILLNESSES (30) AND REMAINS TO DATE A BLACK BOX IN CLINICAL PRACTICE (4). UNDER NORMAL CIRCUMSTANCES, TISSUE MICROCIRCULATORY PERFUSION IS LARGELY HOMOGENOUS AND ADAPTIVE TO SERVE A BALANCE BETWEEN OXYGEN SUPPLY AND DEMAND. HOWEVER, DISEASES LIKE SEPSIS OR ISCHEMIA-REPERFUSION INJURY ARE PARALLELED BY MICROCIRCULATORY DISTURBANCES WITH INCREASED REGIONAL HETEROGENEITY OF PERfusion (4, 24) CHARACTERIZED BY A COMBINATION OF CAPILLARIES WITH LOW BLOOD FLOW AND CAPILLARIES WITH EXTREMELY HIGH BLOOD VELOCITIES (16, 31).

Microcirculatory heterogeneity of flow leads to impaired tissue oxygen extraction (20, 31) and is associated with unfavorable outcome in multiple patient populations (10, 28, 39, 44). Hyperdynamic capillary blood flow theoretically causes inefficient red blood cell (RBC) offloading and therefore provides a functional arteriovenous shunt of oxyhemoglobin (22). A specific feature of cardiopulmonary bypass (CPB) is an instant onset of a nonphysiological, high-flow, low-resistance circulation, similar to the hemodynamic features observed in septic shock (1). Moreover, we previously showed that acute disturbances in microcirculatory perfusion take place after onset of CPB (30). Reduced systemic vascular resistance in combination with a high systemic blood flow and acute hemodilution might predispose for hyperdynamically perfused capillaries.

We hypothesized that acute CPB-induced hemodynamic disturbance leads to increased microcirculatory heterogeneity, with simultaneous hyperdynamically perfused capillaries and altered oxygen-offloading parameters. To investigate our hypothesis, we performed sublingual microcirculatory video microscopy in patients undergoing CPB. Patients undergoing cardiac surgery without CPB served as the control group. Because the influence of systemic hemodynamics on the microcirculation cannot be ruled out, we also focused on the relationship between the systemic and the microcirculation hemodynamics.

MATERIALS AND METHODS

Study design. The present investigation was a single-center, prospective observational study performed in the operation theater and at the intensive care unit (ICU) of the VU University Medical Center. The study was executed in accordance with the Declaration of Helsinki and was approved by the University Human Subjects Committee. Written informed consent was obtained from all patients before inclusion. Patients between 40 and 85 years of age scheduled for elective coronary bypass graft surgery with (n = 18) or without (n = 13) CPB were eligible for study inclusion. Exclusion criteria were reoperations, emergency operations, insulin-dependent diabetes mellitus, body mass index >35 kg/m², and a preoperative hemoglobin level <5.5 mmol/L. No preoperative selection on patient characteristics was applied for allocation to either off-pump or on-pump surgery. The use of CPB was based on the operating schedule, since all off-pump surgical procedures were performed by a single cardiothoracic surgeon. Study inclusion took place only after patients were...
allocated to a surgical technique and therefore did not influence group composition.

Anesthesia. Anesthesia was induced in all patients with 1–3 μg/kg intravenous sufentanil, 0.1 mg/kg midazolam, and 0.1 mg/kg pancuronium bromide, whereas maintenance occurred with a continuous infusion of propofol (200–400 mg/h). Patients were ventilated with tidal volumes of 6–8 ml/kg and a frequency set to obtain an end-tidal CO₂ concentration of between 4 and 5%, with a fraction of inspired oxygen of 0.45. A positive end-expiratory pressure of 5 cmH₂O was applied. After induction of anesthesia, patients received 1 mg/kg dexamethasone and 1,000 mg cefazolin. A pulmonary artery catheter was inserted in all patients as part of the study protocol. Administration of vasoactive medication (nitrroglycerine and dopamine on continuous infusion or bolus administration of phenylephrine, all if necessary) was based on the decision of the anesthesiologist.

CPB group. An S5 heart-lung machine (Stöckert Instrumente, Munich, Germany) with a nonpulsatile centrifugal pump (Delphi, Terumo Europe, Leuven, Belgium) with heparin-coated extracorporeal circuit (Medtronic, Minneapolis, MN) primed with a total of 1,400 ml nonblood priming solution were used for CPB as previously described. (29).

Heparin was administered (300 IU/kg) before cannulation of the ascending aorta and the right atrium to achieve an activated clotting time of 480 s. The blood flow during mild hypothermic (34–35°C) CPB was kept between 2.2 and 3.1 l/min·m⁻². Target mean arterial pressure (MAP) was 60 mmHg. A cell-saver suction device was used to retransfuse washed pericardial shed blood. After weaning from the extracorporeal circulation, protamine was administered to reverse heparin in a 1:1 ratio.

Off-pump group. Before grafting, an initial heparin dose of 300 IU/kg was administered; activated clotting time was maintained throughout the procedure above 380 s. Patients were kept normothermic throughout surgery. To prevent major hemodynamic alterations during grafting, cardiac position was accepted only when systolic blood pressure was higher than 70 mmHg and mixed venous oxygen saturation remained above 60%. A cell-saver suction device was used to retransfuse washed pericardial shed blood.

Microcirculatory imaging. Videomicroscopy of the sublingual microcirculation was performed with a Sidestream Dark Field (SDF) camera (Microscan Video Microscope; Microvision Medical, Amsterdam, The Netherlands). The SDF technique is a technique based on the absorbance spectrum of hemoglobin used to visualize RBCs in microvessels that are localized close to the surface (19). Sublingual microcirculatory perfusion was measured at three consecutive time points: after induction of anesthesia (preoperative), during aortic cross-clamp time in surgery with CPB or during distal grafting in off-pump surgery (intraoperative), and in the first hour after admission to the ICU (postoperative; Fig. 1). Each measurement consisted of three video recordings of 20 s each at three different sublingual sites.

Microcirculatory analysis. Video clips were analyzed with automatic vascular analysis software (AVA 3.0; Microvision Medical) for the microcirculatory flow profile. All analyses were performed by one of the authors; one-third of the video clips was randomly reviewed by one of the other authors for conformation, both blinded for group allocation. The video screen was divided into four quadrants. Subsequently, quadrants were scored for the microvascular flow index (MFI), a semiquantitative scoring scale for the quality of the microvascular flow pattern, ranging from 0 to 3: no flow, sluggish flow, intermittent flow, and continuous flow, respectively (11).

Capillary RBC velocities were determined in all video recordings of a random subset of five patients per group to objectify hyperdynamic microcirculatory perfusion. In each video, the RBC velocity of 10 perfused capillaries was quantified in space-time diagrams as previously described (2), or, above maximal velocity detection by space-time diagrams, the distance of frame-by-frame displacement of RBCs or leukocytes was determined to calculate the velocity (40). For each vessel, the average of multiple velocity determinations was registered. Capillaries were selected based on their position; most centrally located capillaries were included first, as assessed by using De Backer grid line crossings (11). Care was taken to exclude possible arterioles from velocity quantification by assessing the morphology of the microvascular bed. The fraction of hyperdynamic capillaries in quantitative analysis was assessed using a threshold at the 100th percentile of RBC velocities observed preoperatively.

Additionally, the magnitude of hyperdynamic microcirculatory perfusion was determined semiquantitatively in all patients by determination of the number of quadrants per recording with predominantly hyperdynamic capillaries. Required for semiquantitative classification as hyperdynamic vessels were both 1) flashing intensity through rapid leukocyte passage and 2) difficulty to determine flow direction with the bare eye.

To assess microcirculatory heterogeneity semiquantitatively in all patients, the heterogeneity index was used. Heterogeneity index is calculated by dividing the range of MFI scores between quadrants by the mean MFI score, as previously used by Trzeciak et al. (44).

Data collection of hemodynamics and oxygenation parameters. Arterial and mixed venous blood gas analysis were performed at all time points, followed by thermodilution cardiac output measurement and registration of MAP and central venous pressure (CVP) to calculate the hemodynamic and oxygenation parameters as described below. During CPB, mixed venous blood was obtained from the pulmonary artery catheter, and pump flow was used for calculations instead of cardiac index. The following formulas were used:

\[
\text{CAO}_2 = \text{hemoglobin concentration (mmol/1)} \times 1.39 \times (\text{ml O}_2 / \text{dl of blood}) \times \frac{\text{SaO}_2 + \text{PaO}_2}{0.0031};
\]

\[
\text{CVO}_2 = \text{hemoglobin concentration (mmol/1)} \times \frac{1.39 \times \text{SvO}_2 + \text{PvO}_2}{0.0031};
\]

\[
\text{DO}_2 = \text{CAO}_2 \times 10 = \left( \text{conversion} \frac{\text{ml O}_2}{\text{dl of blood}} \text{to ml O}_2/\text{1 of blood} \right) \times \text{cardiac index};
\]

\[
\text{VO}_2 = (\text{CAO}_2 - \text{CVO}_2) \times 10 \times \text{cardiac index};
\]

\[
\text{O}_2\text{ER} = \frac{\text{VO}_2}{\text{DO}_2};
\]

\[
\text{SVRI} = (\text{MAP} - \text{CVP}) \times 80 / \text{Cl}.
\]

where \(\text{CAO}_2\) is arterial content O₂ (ml O₂/dl of blood), \(\text{CVO}_2\) is venous content O₂ (ml O₂/dl of blood), \(\text{CAO}_2 - \text{CVO}_2\) is arteriovenous difference in oxygen content, \(\text{DO}_2\) is oxygen delivery; \(\text{VO}_2\) is oxygen consumption; \(\text{O}_2\text{ER}\) is oxygen extraction ratio; and \(\text{SVRI}\) is systemic vascular resistance index.

Statistical analysis. Data were analyzed by the SPSS statistical software package (version 17.0). All values are expressed as means ± SD or median with interquartile range. A Chi square test was used to test ordinal parameters. Student’s t-test was used to test between groups for parametric variables. For nonparametric parameters, be-
tween-group differences at individual time points were analyzed with a Mann Whitney U-test. For within-group differences, paired t-tests or Wilcoxon tests were used as appropriate. Spearman rho correlation coefficients were calculated to assess relationships between systemic variables and the number of hyperdynamic quadrants or the heterogeneity index as microcirculatory parameters. A P value below 0.05 was considered as indicative of a statistically significant difference. Effect size was calculated ($r = Z \sqrt{N}$) when bordering significance was encountered.

RESULTS

Patient characteristics. Patient characteristics are presented in Table 1. No differences in preoperative parameters were observed between patients undergoing CPB or off-pump surgery, except for increased heparin and protamine administration in patients undergoing CPB.

Hemodynamic data. MAP dropped ~15 mmHg during surgery compared with the preoperative period in both groups. This occurred in parallel with an increase in cardiac index in the CPB group only (Fig. 2). Postoperatively, MAP remained reduced in the CPB group, whereas it restored in the off-pump group. In line with systemic vascular resistance, blood hematocrit declined in the CPB group with one-third after onset of extracorporeal circulation. A minor decrease in hematocrit was detected in the off-pump group. Body temperature was reduced from 36.4 ± 0.6°C to 35.0 ± 0.7°C (P < 0.001) during CPB and was restored postoperatively to 36.5 ± 0.2°C. In the off-pump group, mean preoperative temperature was 36.3 ± 0.6°C and showed a slight increase to 36.6 ± 0.5°C (P = 0.005 vs.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>CPB Surgery (n = 18)</th>
<th>Off-Pump Surgery (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>68 ± 8</td>
<td>62 ± 9</td>
<td>0.074</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>15 (83%)</td>
<td>12 (92%)</td>
<td>0.245</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>0.624</td>
</tr>
<tr>
<td>Median Euroscore</td>
<td>3 (2–5)</td>
<td>3 (1–4)</td>
<td>0.236</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors (n)</td>
<td>18 (100%)</td>
<td>13 (100%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline creatinine, μmol/l</td>
<td>81 ± 19</td>
<td>88 ± 36</td>
<td>0.481</td>
</tr>
<tr>
<td>Baseline hematocrit, %</td>
<td>0.40 ± 0.03</td>
<td>0.42 ± 0.04</td>
<td>0.210</td>
</tr>
<tr>
<td>Baseline leukocyte count, ×10⁹/l</td>
<td>7.6 ± 1.8</td>
<td>7.9 ± 1.6</td>
<td>0.316</td>
</tr>
<tr>
<td>Baseline thrombocyte count, ×10⁹/l</td>
<td>247 ± 61</td>
<td>293 ± 107</td>
<td>0.148</td>
</tr>
<tr>
<td>Median coronary grafts (n)</td>
<td>4 (3–4)</td>
<td>4 (3–5)</td>
<td>0.950</td>
</tr>
<tr>
<td>Surgical duration, min</td>
<td>264 ± 45</td>
<td>249 ± 45</td>
<td>0.383</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>113 ± 29</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Total intraoperative heparin dose, mg</td>
<td>509 ± 276</td>
<td>271 ± 82</td>
<td>0.006</td>
</tr>
<tr>
<td>Protamine dose, mg</td>
<td>386 ± 87</td>
<td>257 ± 122</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means ± SD, medians (interquartile range), or no. of patients (percentage). CPB, cardiopulmonary bypass; n, number; NS, not significant.

Fig. 2. Systemic parameters in patients undergoing cardiac surgery with or without CPB. A: mean arterial pressure. B: cardiac index. C: systemic vascular resistance. D: hematocrit. Intraop, intraoperative; Preop, preoperative; Postop, postoperative. Data were tested with Student’s t-test or paired t-test for between- or within-group comparison, respectively. **P < 0.01 and ***P < 0.001.
preoperative) and 37.0 ± 0.4°C (P < 0.001 vs. preoperative) intraoperative and postoperative, respectively. Preoperative lactate levels were at 1.1 ± 0.3 and 1.0 ± 0.5 mmol/l (P = 0.50 between groups) before on-pump and off-pump surgery, respectively. Postoperative lactate concentration of 1.6 ± 0.7 mmol/l (CPB) and 1.3 ± 0.4 mmol/l (off-pump, P = 0.23 between groups) was not different between groups. No difference in administration of dopamine, nitroglycerine, or phenylephrine was observed between groups (Table 2).

**Microcirculatory flow profile.** The median preoperative MFI was 3.0 (2.6–3.0) and declined to 2.7 (2.4–3.0) (P = 0.069; intraoperative) and 2.5 (2.0–2.9) (P = 0.049, r = 0.46; postoperative) in the CPB group. There were no alterations in MFI during off-pump surgery observed, with median MFI at 2.9 (2.8–3.0), 2.9 (2.8–3.0) (P = 0.674 vs. preoperative), and 2.9 (2.8–3.0) (P = 0.352 vs. preoperative), respectively.

The semiquantitative indexes of microcirculatory heterogeneity (Fig. 3A) and hyperdynamic microcirculatory perfusion (Fig. 3B) increased substantially after onset of CPB. There were no alterations in the microcirculatory flow profile observed in the group undergoing off-pump procedures (Fig. 3). The microcirculatory flow profile remained disturbed after weaning from extracorporeal circulation in the CPB group. This occurred in parallel with an augmented cardiac index and reduced levels of hematocrit, systemic vascular resistance, and MAP. Microcirculatory perfusion remained stable in the off-pump group throughout the perioperative period.

**Quantification of capillary RBC velocity.** Preoperative capillary RBC velocity analysis revealed no difference between the CPB group [369 (191–678 μm/s)] and the off-pump group [413 (220–750 μm/s); P = 0.56]. CPB was associated with increased median velocities compared with the off-pump procedure [1,600 (899–2,500 μm/s) vs. 380 (190–480 μm/s); P < 0.001], and this persisted during the postoperative measurement (Fig. 4).

The 100th percentile of all capillary RBC velocities preoperatively was 2,000 μm/s. The percentage of capillaries that were hyperdynamic (defined as higher RBC velocity than the 100th percentile preoperatively) increased during CPB to 31% of all capillaries (maximal RBC velocity 6,750 μm/s) and after CPB to 29% of all capillaries (maximal RBC velocity 7,350 μm/s). In the off-pump group, no hyperdynamic capillaries were observed (0% during surgery and 1% postoperatively; P < 0.001 between groups for both time points). Examples of regular (video 1) and hyperdynamic (video 2) microcirculatory flow are included as supplemental files (Supplemental data for this article can be found on the American Journal of Physiology: Heart and Circulatory Physiology website.).

**Oxygenation parameters.** In parallel with the development of increased microcirculatory heterogeneity and hyperdynamic capillary perfusion, the arteriovenous difference in blood oxygen content diminished after onset of CPB by 50%, and remained reduced postoperatively (Table 3). Moreover, mixed venous O₂ saturation increased, even though acute hemodilution caused a decline in oxygen delivery. Systemic oxygen consumption declined from 72 ± 22 to 47 ± 14 ml·min⁻¹·m⁻² (P = 0.002) during CPB, along with reduced oxygen delivery, although the oxygen extraction ratio was low. After weaning from CPB, a recovery of oxygen consumption and delivery was observed, although CA-VO₂ remained diminished. In contrast, oxygenation parameters remained largely unaltered in the off-pump group.

**Correlation of systemic variables with microcirculatory parameters.** Spearman coefficients were calculated to assess associations between systemic variables and hyperdynamic microcirculatory perfusion or the heterogeneity index. Inverse, but weak, correlations of hyperdynamic microcirculatory perfusion with CA-VO₂ (rho = −0.33, P < 0.001) and VO₂ (rho = −0.352 vs. preoperative) were observed.
Fig. 4. Histogram of capillary red blood cell (RBC) velocity, pooled for patients undergoing cardiac surgery with (n = 5) or without (n = 5) CPB.
A microvascular shunting phenomenon as observed in the current investigation has often been hypothesized to exist during critical illness (5, 25, 35, 45). However, to date no such phenomenon has been visualized in humans (15). The presence of hyperdynamic capillaries during septic shock was recently not detected in patients with septic shock (34). Macrocirculatory variables were, however, not hyperdynamic in that investigation, which might have precluded the observation of hyperdynamic microcirculatory perfusion (34). An alternative explanation for the lack of detection of microvascular shunting in the study of Edul et al. (15) may be the prolonged time between onset of disease and microcirculatory observation for patients with sepsis (13, 17). We have demonstrated in the current study that microvascular shunting occurs within an hour after onset of an injurious stimulus, similar to experimental studies that have observed hyperdynamic capillaries (7, 16, 31). It may therefore be conceivable that microvascular shunting is an early phenomenon that may be more difficult to detect with progression of microcirculatory disturbances.

The increase in microcirculatory heterogeneity induced by CPB may lead to impairment of tissue oxygen extraction (16, 24). In the current study, systemic oxygen consumption declined by 35% during CPB in the current study, which could not be explained by mild hypothermia alone (50). Although the exact cause of this large reduction in VO2 remains unknown from the present investigation and a contribution of mitochondrial dysfunction cannot be excluded (3), it is likely that VO2 was limited by microcirculatory heterogeneity due to local mismatching of oxygen supply and demand (20, 24). Low oxygen consumption is associated with an increase in anaerobic CO2 production and increased lactate levels (37). Hyperlactatemia has been associated with increased postoperative morbidity and mortality following cardiac surgery (14) al-

### Table 3. Oxygenation parameters

<table>
<thead>
<tr>
<th></th>
<th>CPB Surgery</th>
<th>Off-Pump Surgery</th>
<th>P Value</th>
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<tbody>
<tr>
<td>SV0₂, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>78 ± 7</td>
<td>80 ± 8</td>
<td>0.593</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>83 ± 5†</td>
<td>75 ± 5</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>75 ± 10</td>
<td>70 ± 10†</td>
<td>0.148</td>
</tr>
<tr>
<td>CA-VO₂, ml/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>3.6 ± 1.1</td>
<td>3.6 ± 1.4</td>
<td>0.998</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>1.8 ± 0.6†</td>
<td>4.1 ± 1.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.7 ± 1.0†</td>
<td>4.5 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>DO₂, ml·min⁻¹·m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>347 ± 77</td>
<td>412 ± 113</td>
<td>0.119</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>281 ± 32†</td>
<td>409 ± 120</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>318 ± 98</td>
<td>504 ± 101</td>
<td>0.000</td>
</tr>
<tr>
<td>VO₂, ml·min⁻¹·m⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>72 ± 22</td>
<td>89 ± 32</td>
<td>0.152</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>47 ± 14†</td>
<td>102 ± 22</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>71 ± 23</td>
<td>117 ± 20</td>
<td>0.000</td>
</tr>
<tr>
<td>O₂ER, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>22 ± 7</td>
<td>20 ± 6</td>
<td>0.680</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>17 ± 5†</td>
<td>24 ± 4</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative</td>
<td>24 ± 9</td>
<td>24 ± 3</td>
<td>0.926</td>
</tr>
</tbody>
</table>

Values are means ± SD. CA-VO₂ is arteriovenous oxygen content difference; DO₂ is oxygen delivery; O₂ER is oxygen extraction ratio; SV0₂ is mixed venous oxygen saturation; and VO₂ is oxygen consumption. †P < 0.05 vs. preoperative.

−0.27, P = 0.008) were detected. Moreover, a reduction in hematocrit was associated with a moderate increase in hyperdynamic quadrants (Spearman’s rho = −0.51, P < 0.001) and weak alteration in the heterogeneity index score (rho = −0.28, P = 0.001). No correlations with other hemodynamic or blood gas-derived variables or administered vasoactive medication were observed.

**Postoperative outcome.** ICU stay was 1 (1–1) and 1 (1–1) in on-pump and off-pump groups, respectively (P = 0.798). Two patients in the CPB group developed postoperative acute kidney injury (AKI), one of which died three weeks postoperatively, whereas the other patient regained preexistent renal function. No AKI or mortality was observed in the off-pump group (P = 0.497 for AKI, P = 1.000 for mortality between groups). Both patients developing AKI showed increased postoperative (+0.63 and +0.56) and postoperative (+1.38 and +0.59) heterogeneity index and decreased postoperative MFI scores (−1.04 and −0.47) compared with preoperative values. New-onset postoperative atrial fibrillation developed in two patients undergoing on-pump surgery and in one patient undergoing off-pump surgery (P = 1.000 between groups). No myocardial or cerebral infarction occurred in the current study population.

**DISCUSSION**

This study is the first to show that the onset of CPB induces acute microcirculatory flow alterations, with increased microcirculatory heterogeneity and a large fraction of hyperdynamically perfused capillaries, both persisting in the early postoperative phase. Quantification of capillary blood velocity during CPB revealed high flow rates, associated with a reduction in systemic oxygen extraction. These observations were absent in patients undergoing off-pump cardiac surgery.

Normal capillary RBC velocities may differ considerably within and between tissues but are generally thought to range between 100 and 800 μm/s, with a maximum of 1,600 μm/s (21, 27, 31, 46). The threshold we currently applied for hyperdynamic capillaries was based on the maximum RBC velocity observed preoperatively, at 2,000 μm/s, well above normal levels. During and after cardiac surgery with CPB, almost one-third of the capillaries are perfused at very high velocities, whereas we found no hyperdynamic capillaries in off-pump surgery. To our best knowledge, capillary blood velocities up to 7,350 μm/s have not been reported in the literature. It is conceivable that the concomitant shear stresses may inflict damage to the capillary endothelium or the endothelial glycocalyx and subsequently contribute to obstructed capillaries (49, 51).

High capillary blood velocities limit oxygen exchange and thus cause systemic arteriovenous shunting of oxygenated hemoglobin (22). Despite a marked hemodilution and a reduced MFI, CA-VO₂ diminished by 50% during CPB in the current study. The reduction in CA-VO₂ occurred both intra- and postoperatively in parallel with an increased number of capillaries demonstrating flow velocities that cannot support adequate RBC oxygen offloading. Additionally, an inverse correlation between CA-VO₂ and hyperdynamic capillaries was detected. In line with the current results, a previous investigation by our group showed that the onset of extracorporeal circulation led to an immediate increase in microvascular hemoglobin saturation, reflecting reduced microcirculatory oxygen extraction (2). Our current observations therefore support the existence of microvascular shunting through high-velocity capillaries in a patient population undergoing CPB.
though this was not observed in the current population with low Euroscores. More complex cardiac surgery with longer CPB duration is associated with increased postoperative morbidity and mortality, and patients undergoing these procedures are thus likely to have more severe microcirculatory impairment. The work of Trzeciak et al. supports the association between microcirculatory failure and poor outcome, since the heterogeneity index in the microcirculation early in the course of septic shock was predictive of mortality (44). The relationship between microcirculatory disturbances and poor clinical outcome was confirmed in several patient populations (10, 28, 39), but this has not yet been established for cardiac surgery. We currently did observe deterioration of microvascular perfusion parameters in the two patients developing AKI, but the current study was not designed to detect a relationship with clinical outcome.

Our observation may be an important factor in explaining several clinical observations on oxygenation parameters as the difference between microvascular and venous \( pO_2 \) values observed in critical disease states (26, 42). Moreover, we demonstrate that microcirculatory alterations can hinder the clinical interpretation of \( SV_O_2 \), since previously it has been demonstrated that venous hyperoxia after CPR is associated with poor outcome (38). This is supported by recent reports on ICU patients by Velissaris et al. in which high \( SV_O_2 \) levels were not indicative of adequately optimized circulatory management (47) and by Monnet and coworkers showing that \( SV_O_2 \) could not predict increased oxygen consumption after an intravascular volume expansion in fluid responders (33). Most illustrative is the recent study by Pope and colleagues in patients admitted to the emergency department showing that high central venous oxygen saturation is associated with increased mortality, hypothetically through microcirculatory failure (35). Finally, a possibly erroneous interpretation of \( SV_O_2 \) values should be taken into account when using it as a RBC transfusion trigger for cardio surgical patients (36).

Although several factors might theoretically be responsible for the alterations of the microcirculatory flow profile during CPB, the current study does not differentiate between the different causes. A one-third reduction in systemic vascular resistance was observed after onset of CPB. During arteriolar vasodilation, a reduction in blood pressure drop over the resistance vessels leads to a higher pressure difference over the capillary bed (43), which may theoretically increase the number of hyperdynamically perfused capillaries. However, the relationship between macrocirculatory parameters and microcirculatory perfusion has been found to be loose in multiple investigations (12), and the contribution of a reduction in systemic vascular resistance to microvascular perfusion patterns may therefore be questionable. Increased microcirculatory heterogeneity is hypothesized to be a sign of impaired vascular reactivity (16), a phenomenon that is known to occur during CPB (18), and may be aggravated by nonpulsatile flow as is present during CPB (34). Previously, we have found that pulsatile flow during CPB is associated with improved recovery of perfused microvascular density (30), but the effect of pulsatility on vasoreactivity or microcirculatory heterogeneity is still unknown. Finally, acute hemodilution during onset of CPB contributes to reduced resistance to blood flow due to its decrease in blood viscosity. We found that reduced hematocrit was correlated to both increased heterogeneity and hyperdynamic capillary perfusion in the current study. In experimental observations, however, hemodilution alone caused a maximum of 40% increase in arteriolar blood velocity (8), and capillary velocity never exceeded 2,000 \( \mu \)m/s at hematocrit levels down to 0.20 l/l (23). Miniaturized extracorporeal circulation systems cause less hemodilution than conventional systems, but the associated reduction in hemodilution led to only a minor improvement in microcirculatory perfusion (52). Hemodilution as observed in the current population may therefore contribute to microcirculatory disturbances, but only to a minor extent.

The current study is limited by the highly regional microcirculatory measurement method. Although it has been challenged (6), most studies have found that the sublingual microvascular perfusion is closely correlated to the visceral microvasculature (9, 32, 48). Moreover, all microvascular beds are exposed to the same hemodynamic alterations during the study period, and the disturbances in whole body oxygenation parameters suggest that the current observations are a systemic phenomenon.

In conclusion, the current study provides the first direct human evidence for a systemic microvascular shunting phenomenon following acute physiological disturbances, as occurs after onset of CPB but not during off-pump surgery. A hypothesis of impaired oxygen extraction caused by hyperdynamic capillaries was supported by reduced blood arteriovenous oxygen difference and low systemic oxygen extraction. This observation increases the understanding of acute microcirculatory pathophysicsology, which is necessary before interventions to preserve microcirculatory perfusion can be examined. The mechanism by which these microcirculatory alterations develop are still to be investigated. Additionally, it remains to be elucidated whether an acute induction of microcirculatory heterogeneity and arteriovenous shunting by CPB is associated with increased morbidity or mortality.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, relevant to the current study are declared by the authors.

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


17. H974 SYSTEMIC MICROVASCULAR SHUNTING FOLLOWING CPB


