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

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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.

The current study provides the first direct human evidence for a microcirculatory 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

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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 tidal volumes of 6–8 ml/kg and a frequency set to obtain an end-tidal ronium bromide, whereas maintenance occurred with a continuous intravenous sufentanil, 0.1 mg/kg midazolam, and 0.1 mg/kg pancu-

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CPB group. An S5 heart-lung machine (Stöckert Instrumente, Munich, Germany) with a nonpulsatile centrifugal pump (Delphin, 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 3.0 l min⁻¹m⁻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 hyperdy-
namic 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 predominately 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 Trzcziak 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:

\[ \text{CAO}_2 = \text{hemoglobin concentration (mmol/1)} \times 0.6206 \text{ (conversion mmol/1 to g/dl hemoglobin)} \times 1.39 \text{ (ml O}_2/\text{g of hemoglobin)} \times (S\text{aO}_2 + P\text{aO}_2 - 0.0031); \]

\[ \text{CVO}_2 = \text{hemoglobin concentration (mmol/1)} \times 0.6206 \times 1.39 \times S\text{vO}_2 + P\text{vO}_2 - 0.0031; \]

\[ \text{CA}_\text{O}_2 - \text{vO}_2 = \text{CAO}_2 - \text{CVO}_2; \]

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

\[ \text{V}_0 = (\text{CAO}_2 - \text{CVO}_2) \times 10 \times \text{cardiac index}; \]

\[ \text{O}_2\text{ER} = \text{V}_0/\text{DO}_2; \]

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

where \( \text{CAO}_2 \) is arterial content \( \text{O}_2 \) (ml O₂/dl of blood), \( \text{CVO}_2 \) is venous content \( \text{O}_2 \) (ml O₂/dl of blood), \( \text{CA}_\text{O}_2 - \text{vO}_2 \) is arteriovenous difference in oxygen content, \( \text{DO}_2 \) is oxygen delivery; \( \text{V}_0 \) 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/√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°C to 35.0°C (P<0.001) during CPB and was restored postoperatively to 36.5°C. In the off-pump group, mean preoperative temperature was 36.3°C and showed a slight increase to 36.6°C (P=0.005 vs.

![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.](http://ajpheart.physiology.org/)

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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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, l/l</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>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.
 SYSTEMIC MICROVASCULAR SHUNTING FOLLOWING CPB

Table 2. Vasoactive medication

<table>
<thead>
<tr>
<th></th>
<th>CPB Surgery</th>
<th>Off-Pump Surgery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6 (33)</td>
<td>7 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>5 (28)</td>
<td>7 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative</td>
<td>13 (72)</td>
<td>7 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Nitroglycerine n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6 (33)</td>
<td>3 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>7 (39)</td>
<td>3 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative</td>
<td>12 (66)</td>
<td>4 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Phenylephrine, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6 (33)</td>
<td>4 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>4 (22)</td>
<td>2 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2 (11)</td>
<td>2 (15)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are no. of patients (percentage). Data were tested with the $\chi^2$-test.

preoperative) and $37.0 \pm 0.4^\circ{C}$ ($P < 0.001$ vs. preoperative) intraoperative and postoperative, respectively. Preoperative lactate levels were at $1.1 \pm 0.3$ and $1.0 \pm 0.5$ mmol/l ($P = 0.50$ between groups) before on-pump and off-pump surgery, respectively. Postoperative lactate concentration of $1.6 \pm 0.7$ mmol/l (CPB) and $1.3 \pm 0.4$ 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 $\mu$m/s)] and the off-pump group [413 (220–750 $\mu$m/s); $P = 0.56$]. CPB was associated with increased median velocities compared with the off-pump procedure (1,600 (899–2,500 $\mu$m/s) vs. 380 (190–480 $\mu$m/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 $\mu$m/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 $\mu$m/s) and after CPB to 29% of all capillaries (maximal RBC velocity 7,350 $\mu$m/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 blood 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 $O_2$ saturation increased, although venous $O_2$ content 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 $CA-O_2$ 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 $CA-O_2$ (rho = −0.33, $P < 0.001$) and $VO_2$ (rho = 0.20, $P < 0.001$) were observed. However, this relation was not observed for the heterogeneity index. Moreover, the correlation of systemic variables with microcirculatory perfusion or the heterogeneity index remained small and unaltered during and after the surgical procedures. The correlation of systemic variables with microcirculatory perfusion or the heterogeneity index was not statistically significant.

Fig. 3. Sublingual microcirculatory parameters of heterogeneity and hyperdynamic perfusion. A: heterogeneity index. B: hyperdynamic microcirculatory perfusion. Data were tested with Mann Whitney U-test or Wilcoxon test for between- or within-group comparison, respectively. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. 

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Fig. 4. Histogram of capillary red blood cell (RBC) velocity, pooled for patients undergoing cardiac surgery with (n = 5) or without (n = 5) CPB.
undergoing off-pump surgery (patients undergoing on-pump surgery and in one patient un-

New-onset postoperative atrial fibrillation developed in two

1.04 and 0.59) heterogeneity index and decreased postoperative MFI

groups). Both patients developing AKI showed increased in-

P

preoperative.

gas-derived variables or administered vasoactive medication

Dynamic quadrants (Spearman’s rho

0.27,

0.008) were detected. Moreover, a reduction in

hematocrit was associated with a moderate increase in hyper-

dynamic 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 kid-

ney injury (AKI), one of which died three weeks postopera-
tively, 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 in-
traoperative (+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 un-
dergoing 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 micro-
circulatory heterogeneity and a large fraction of hyperdynamically

perfused capillaries, both persisting in the early postopera-
tive 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 endo-
thelial 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 re-
duced 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 capil-

laries demonstrating flow velocities that cannot support ade-

quate RBC oxygen offloading. Additionally, an inverse cor-

relation between CA-VO2 and hyperdynamic capillaries was
detected. In line with the current results, a previous investiga-

tion by our group showed that the onset of extracorporeal circu-

lation led to an immediate increase in microvascular hemoglobin

saturation, reflecting reduced microcirculatory oxygen extrac-

tion (2). Our current observations therefore support the exist-

ence of microvascular shunting through high-velocity capil-

laries in a patient population undergoing 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). Macrocircula-
tory variables were, however, not hyperdynamic in that inves-
tigation, which might have precluded the observation of hy-

perdynamic 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 experimen-
tal studies that have observed hyperdynamic capillaries (7, 16,

31). It may therefore be conceivable that microvascular shunt-

ing 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 de-

clined 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 mitochon-
drial 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 anaero-
bic CO2 production and increased lactate levels (37). Hyper-
lactatemia 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>
</tr>
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<tbody>
<tr>
<td>SVO2, %</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 ± 4†</td>
<td>75 ± 5</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>75 ± 10</td>
<td>70 ± 9†</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</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.7 ± 1.0†</td>
<td>4.5 ± 6.6</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>
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<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 differ-

dence; DO2 is oxygen delivery; O2ER is oxygen extraction ratio; SVO2 is mixed

venous oxygen saturation; and VO2 is oxygen consumption. †P < 0.05 vs.

preoperative.
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 pO2 values observed in critical disease states (26, 42). Moreover, we demonstrate that microcirculatory alterations can hinder the clinical interpretation of S\text{vO2}, since previously it has been demonstrated that venous hyperaoxia after CPR is associated with poor outcome (38). This is supported by recent reports on ICU patients by Velissaris et al. in which high S\text{vO2} levels were not indicative of adequately optimized circulatory management (47) and by Monnet and coworkers showing that S\text{vO2} 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 S\text{vO2} values should be taken into account when using it as a RBC transfusion trigger for cardiothoracic 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 pathophysiology, 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.

GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: N.J.K., P.A., C. Baufreton, and C. Boer conception and design of research; N.J.K. and L.E.S. performed experiments; N.J.K., L.E.S., and C. Boer interpreted results of experiments; N.J.K., L.E.S., and C. Boer analyzed data; N.J.K., P.A., C. Baufreton, and C. Boer prepared figures; N.J.K., L.E.S., and C. Boer drafted manuscript; N.J.K., P.A., C. Baufreton, and C. Boer revised manuscript; N.J.K., L.E.S., P.A., C. Baufreton, and C. Boer approved final version of manuscript.

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