Pulsatile flow during cardiopulmonary bypass preserves postoperative microcirculatory perfusion irrespective of systemic hemodynamics

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Koning NJ, Vonk AB, van Barneveld LJ, Beishuizen A, Atasever B, van den Brom CE, Boer C. Pulsatile flow during cardiopulmonary bypass preserves postoperative microcirculatory perfusion irrespective of systemic hemodynamics. J Appl Physiol 112: 1727–1734, 2012. First published March 8, 2012; doi:10.1152/japplphysiol.01191.2011.—The onset of nonpulsatile cardiopulmonary bypass is known to deteriorate microcirculatory perfusion, but it has never been investigated whether this may be prevented by restoration of pulsatility during extracorporeal circulation. We therefore investigated the distinct effects of nonpulsatile and pulsatile flow on microcirculatory perfusion during on-pump cardiac surgery. Patients undergoing coronary artery bypass graft surgery were randomized into a nonpulsatile (n = 17) or pulsatile (n = 16) cardiopulmonary bypass group. Sublingual mucosal microvascular perfusion was measured at distinct perioperative time intervals using sidestream dark field imaging, and quantified as the level of perfused small vessel density and microvascular flow index (vessel diameter < 20 μm). Microcirculation measurements were paralleled by hemodynamic and free hemoglobin analyses. The pulse wave during pulsatile bypass estimated 58 ± 17% of the baseline blood pressure waveform. The observed reduction in perfused vessel density during aorta cross-clamping was only restored in the pulsatile flow group and increased from 15.5 ± 2.4 to 20.3 ± 3.7 mm/mm² upon intensive care admission (P < 0.01). The median postoperative microvascular flow index was higher in the pulsatile group [2.6 (2.5–2.9)] than in the nonpulsatile group [2.1 (1.7–2.5); P = 0.001]. Pulsatile flow was not associated with augmentation of free hemoglobin production and was paralleled by improved oxygen consumption from 70 ± 14 to 82 ± 16 ml·min⁻¹·m⁻² (P = 0.01) at the end of aortic cross-clamping. In conclusion, pulsatile cardiopulmonary bypass preserves microcirculatory perfusion throughout the early postoperative period, irrespective of systemic hemodynamics. This observation is paralleled by an increase in oxygen consumption during pulsatile flow, which may hint toward decreased microcirculatory heterogeneity during extracorporeal circulation and preservation of microcirculatory perfusion throughout the perioperative period.

cardiopulmonary bypass; microcirculation; pulsatile flow; cardiac surgery

EARLIER STUDIES by our group and others have shown that cardiopulmonary bypass (CPB) with nonpulsatile flow is associated with a decrease in capillary density and microvascular flow, most likely as a result of hemodilution, hypothermia, inflammation, and endothelial dysfunction (1, 3, 8). Loss of microcirculatory perfusion during extracorporeal circulation may contribute to the development of organ dysfunction and has been indicated as an independent predictor of outcome (32, 36). Although restoration of pulsatile flow during cardiopulmonary bypass could be beneficial for postoperative outcome, there is an ongoing debate about the mechanisms underlying the favorable effects of pulsatility during extracorporeal circulation (16). Reported advantages of pulsatile cardiopulmonary bypass include preserved renal function, reduced liver damage, reduced levels of endotoxins, less need for inotropics and a lower mortality after surgery (25, 34, 41).

There are only limited data available about the implications of nonpulsatile and pulsatile flow on microcirculatory perfusion during CPB. A recent crossover study by Elbers et al. (10) showed no difference in microcirculatory perfusion after 10 min of either pulsatile or nonpulsatile CPB, but their conclusions were limited by the study design. In contrast, laser-Doppler flow or gastric tonometry measurements indirectly indicated that pulsatility may preserve microvascular perfusion (13, 24, 28). At similar mean arterial pressures, pulsatile flow was associated with a 10–15% more energy equivalent pressure than nonpulsatile flow (37), which has previously been suggested to be a prerequisite to overcome the critical capillary closing pressure (43). Under experimental conditions, nonpulsatile flow further resulted in reduced endothelial shear stress that may contribute to endothelial dysfunction and increased microvascular resistance (35). Others showed that distinct flow conditions affect endothelial nitric oxide synthase expression, prostacyclin and proinflammatory protein production, and the induction of vascular adhesion molecules (22, 27). In particular, pulsatile flow increases endothelial nitric oxide production compared with nonpulsatile flow (21, 26).

It is questioned whether pulsatile flow is indeed associated with preserved microvascular perfusion compared with nonpulsatile flow during extracorporeal circulation. We therefore investigated whether pulsatile flow preserves microvascular perfusion during and after cardiopulmonary bypass in relatively healthy patients undergoing coronary artery bypass graft surgery. Direct microvascular perfusion measurements of the sublingual mucosa were performed during the intraoperative and postoperative period using Sidestream dark-field (SDF) imaging, a video technique that allows direct microscopic observation of the microcirculation (14). We further investigated whether our observations were associated with alterations in blood damage or could be linked to systemic hemodynamic alterations.

MATERIALS AND METHODS

Patient characteristics. The local Human Subjects Committee approved this single-center, prospective clinical study, and written informed consent was obtained from all subjects. The study group included 34 patients undergoing elective coronary artery bypass graft...
(CABG) surgery with cardiopulmonary bypass (CPB). Previous heart surgery, emergency surgery, insulin-dependent diabetes mellitus, and a body mass index \( > 30 \text{ kg/m}^2 \) were considered as exclusion criteria. Clonidine was stopped at 5 days preoperatively, whereas acetylsalicylic acid was continued. Patients were randomized into the nonpulsatile flow or pulsatile flow study group by envelope drawing.

**Anesthesia protocol.** On the day of surgery, coronary patients received their usual early morning dose of antianginal medication and lorazepam (5 mg), whereas no diuretics were given. Anesthesia consisted of sufentanil (3–7 \( \mu \text{g/kg} \)) with pancuronium bromide (0.1 mg/kg) and midazolam (0.1 mg/kg) and was maintained by continuous propofol infusion (5–15 ml/h). Ventilation parameters were 10 ml/kg tidal volume, 4–5% end-tidal CO2, 45% O2-air mixture, positional propofol infusion (5–15 ml/h). &n

**Cardiopulmonary bypass.** An S3 heart-lung machine with heater-cooler device (Stöckert Instrumente GMBH, Munich, Germany) and centrifugal pump (Sarns, Terumo Europe NV, Leuven, Belgium) were used for CPB. The extracorporeal circuit consisted of a heparin-coated polyvinyl tubing system with a hollow fiber oxygenator and arterial line filter (Affinity, Medtronic, Minneapolis, MN), a soft shell venous reservoir (MVR 1600, Medtronic) and a cardiometry reservoir (Intersurgical). The circuit was primed with 1,000 ml modified fluid gelatin (Braun Melsungen AG, Germany), 100 ml mannitol (20%, Baxter BV, Utrecht, Netherlands), 50 ml sodium bicarbonate (8.4% Braun Melsungen AG) and 250 ml lactated Ringer’s solution (Baxter BV), containing 1,000 mg celecoxib (Eli Lilly Nederland BV, Nieuwegein, Netherlands) and 5,000 IU bovine heparin. After heparin (300 IU/kg) administration, the arterial cannula was placed in the ascending aorta and the (two stage) venous cannula (36 French) in the right atrium. Venting of the left ventricle was achieved by an aortic root-cannula. CPB (34°C; 2.2–3.0 l/min \( \text{m}^2 \)) was initiated when the activated clotting time exceeded 480 s. Myocardial protection was achieved with 4°C crystalloid cardioplegia solution (St. Thomas). Patients were weaned from CPB when rectal temperature estimated 36°C. Heparin was reversed with protamine in a 1:1 fashion and recorded on digital tapes for off-line computer analysis.

**Pulsatile or nonpulsatile flow group.** During two phases of extracorporeal circulation without aortic cross-clamp, the centrifugal pump was set to pulsatile during aortic cross-clamp time. The pump used a standard internal algorithm to generate pulsatility with a frequency of 60 per minute. Area under the curve analysis was performed on cycles of the arterial blood pressure waveform to provide a relative quantification of the strength of the arterial pressure wave as measured in the radial artery. Comparisons were made between cycles before CPB and cycles during aortic cross-clamping. During two phases of extracorporeal circulation without aortic cross-clamp, the centrifugal pump was set to the nonpulsatile mode, although surgeons intended to preserve flow through the heart, leading to varying pulsatility at these time points (T2 and T5). In the nonpulsatile flow group standard centrifugal pump settings were used resulting in a continuous, nonpulsatile blood flow.

**SDF imaging.** Sublingual mucosal microcirculation measurements were performed during surgery and at the intensive care unit (ICU) using SDF imaging (MicroScan, Microvision Medical, Amsterdam, Netherlands). SDF and its predecessor, orthogonal polarization spectral (OPS) imaging, have been used extensively in clinically assessing microcirculatory perfusion (1, 3, 5, 7, 8, 10, 32, 36). SDF demonstrated improved capillary contrast and quality compared with the earlier developed OPS imaging technique in a validation study (14).

Briefly, SDF imaging is based on noninvasive hand-held video microscopy with a light guide placed on organ (14). A 5× magnifying lens (field area of \( 1 \text{ mm}^2 \)) projected the image to a video camera inside the device. Microvascular images were observed on a monitor with a final magnification of 350× and recorded on digital tapes for off-line computer analysis.

The images were made after induction of anesthesia (T1; preop), after onset of CPB before cross-clamping the aorta (T2; CPB start), early after cross-clamping the aorta (T3; AoX start), before removing the aortic cross-clamp (T4; AoX end), 5 min after removing the aortic cross-clamp (T5; post-AoX), after weaning from CPB while under anesthesia (T6; post-CPB) and in the first hour after ICU admission (T7; ICU). At each time point, three SDF sequences of 10 s were recorded.

Each video clip was analyzed with automatic vascular analysis software (AVA 3.0, Microvision Medical, Amsterdam), according to the recommendations by De Backer et al. (9). Analyses were performed by one of the authors, and one-third of the video clips were randomly reviewed by two of the other authors to check the inter-rater agreement. All vessels were identified manually, which enabled the software to calculate the total vessel density (TVD) (in mm/mm²). Subsequently, small vessels relevant for oxygen exchange as reflected by a diameter < 20 µm were scored separately using the following classifications: no flow, sluggish flow, intermittent flow, and continuous flow. For the calculation of the perfused vessel density (PVD) (in mm/mm²), the software considered vessels scored with intermittent or no flow as nonperfused, whereas continuous or sluggish scores were regarded as perfused vessels.

For determination of the microvascular flow index (MFI), the screen was divided in four quadrants. The same standard classification as described above was used to explain the predominant flow pattern for an entire quadrant. No flow, sluggish flow, intermittent flow, and continuous flow represented scores from 0 to 3, respectively. The mean score of the four quadrants represented the MFI. The inter- and intra-rater agreement for the microvascular flow index has been shown to be 90% and 85%, respectively (5).

**Blood samples.** Plasma free hemoglobin was assessed before extracorporeal circulation and after nonpulsatile or pulsatile cardiopulmonary bypass (Haemoscan BV, Groningen, The Netherlands). Blood samples drawn upon intensive care unit admission were analyzed for leukocyte count, C-reactive protein (CRP), and creatinine according to routine laboratory procedures. The release of IL-6, vascular endothelial growth factor (VEGF), and TNF-α was determined before CPB, after weaning from CPB, and at ICU using commercially available ELISA kits (BioLegend’s ELISA MAX Deluxe Set, R&D systems). ELISA was performed following the instructions of the manufacturer. Cardiac index was determined by thermodilution cardiac output measurements (at T1, T6, T7) in a subgroup of patients (n = 7, pulsatile CPB: n = 9) and by CPB flows (at T3, T4) in all patients. The oxygen consumption (VO₂), delivery (DO₂) and oxygen extraction ratio (VO₂/DO₂) were calculated at T3 (AoX start) and T4 (AoX end) using the cardiac index derived from CPB flow in combination with arterial and mixed venous blood gas values. The following formulas were used: DO₂ = CaO₂ \times cardiac index; VO₂ = (CaO₂ – CvO₂) \times cardiac index; CaO₂ = hemoglobin \times 1.36/0.6206 \times SaO₂ \times 10 + PaO₂ \times 0.0031; and CvO₂ = hemoglobin \times 1.36/0.6206 \times SvO₂ \times 10 + PaO₂ \times 0.0031, where CaO₂ and CvO₂ are arterial and venous oxygen content, respectively; SaO₂ and SvO₂ are arterial and venous oxygen saturation, respectively; and PaO₂ and PvO₂ are arterial and venous oxygen tension, respectively.

**Statistical analysis.** Data were analyzed using a SPSS statistical software package (version 17.0). All values are expressed as means ± SD or median with interquartile range (IQR). Repeated-measures (RM) ANOVA was performed to analyze between-group effects of parameters with multiple time points (mean arterial pressure, cardiac index, TVD, and PVD). Changes from baseline values and changes during cross-clamp time for temperature, hemoglobin, hematocrit, VO₂,i, DO₂,i, and oxygen extraction ratio were analyzed by a paired t-test; between-group effects were tested by a Student’s t-test. Differences in MFI were tested for individual time points using a Mann-Whitney U test. P < 0.05 was considered as statistically significant.
RESULTS

**Intraoperative and postoperative hemodynamics.** After exclusion of one patient due to a large variation in intraoperative and microcirculatory data, the study population included 33 patients for final analysis. Figure 1 represents typical examples of arterial blood pressure waveforms for nonpulsatile and pulsatile flow in individual patients. Area-under-curve analysis of the arterial blood pressure waveforms in eight subjects revealed a pulse wave during the pulsatile flow mode with an area under the curve of $58 \pm 17\%$ of the pulse wave during systemic circulation before cardiopulmonary bypass. In the nonpulsatile flow mode, the area under the curve estimated $0 \pm 0\%$ from baseline ($n = 3$).

Patient characteristics are presented in Table 1. Repeated-measures ANOVA revealed no differences in mean arterial blood pressure values (Fig. 2A; $P = 0.35$) and cardiac index (Fig. 2B; $P = 0.25$) over time between nonpulsatile and pulsatile flow groups. Cardiopulmonary bypass was associated with a decrease in body temperature, hemoglobin and hematocrit, but we found no differences between groups (Table 2). In a subgroup of patients with a pulmonary artery catheter we observed an immediate decrease in the oxygen consumption index in both groups upon the start of extracorporeal circulation. Figure 3 shows the oxygen delivery index (DO$_2$i; A), oxygen consumption index (VO$_2$i; B), and oxygen extraction ratio (C) for the nonpulsatile and pulsatile groups at the beginning (AoX start) and end of aortic cross-clamping (AoX end). There were no alterations in DO$_2$i in both groups, whereas the VO$_2$i ($69.8 \pm 13.8\%$ vs. $82.4 \pm 15.6\%\text{ mLO}_2\text{ m}^{-2}\text{ min}^{-1}$; paired $t$-test $P = 0.01$) and oxygen extraction ratio ($0.23 \pm 0.05$ vs. $0.26 \pm 0.04$; paired $t$-test $P = 0.035$) were increased at the end of aortic cross-clamping (AoX end) in the pulsatile flow group compared with baseline (AoX start).

**Microcirculatory perfusion.** Figure 4 shows the sublingual total microcirculatory vessel density (TVD; A) and the perfused microcirculatory vessel density (PVD; B) for vessels smaller than 20 $\mu$m. In both nonpulsatile and pulsatile groups, the TVD reduced by 20% during aortic cross-clamping (AoX end) compared with baseline (Preop). The decline in TVD tended to be transient in the pulsatile flow group, but this restoration was not significantly different from the laminar flow group (repeated-measures ANOVA; $P = 0.13$). The observed reduction in perfused vessel density (PVD) during aorta cross-clamping was only restored in the pulsatile flow group and increased from $15.5 \pm 2.4$ to $20.3 \pm 3.7$ mm/mm$^2$ upon intensive care admission in this group (repeated-measures ANOVA; $P = 0.02$). The perfused vessel density remained at a stable level in the nonpulsatile flow group until ICU admission. The effect of pulsatile flow on the microvascular flow index (MFI) is depicted in Fig. 5 for small vessels. Starting from the end of aortic cross-clamping (AoX end), the MFI significantly restored in the pulsatile group compared with nonpulsatile flow. The median postoperative microvascular

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Nonpulsatile Flow</th>
<th>Pulsatile Flow</th>
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<tr>
<td>$n$</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Age, yr</td>
<td>$65 \pm 7$</td>
<td>$67 \pm 11$</td>
</tr>
<tr>
<td>Males, $n$ (%)</td>
<td>14/17 (82%)</td>
<td>10/16 (63%)</td>
</tr>
<tr>
<td>BSA, m$^2$</td>
<td>2.1 $\pm$ 0.2</td>
<td>1.9 $\pm$ 0.2</td>
</tr>
<tr>
<td>Diabetes mellitus II, $n$ (%)</td>
<td>2/17 (12%)</td>
<td>4/16 (25%)</td>
</tr>
<tr>
<td>Antihypertensive treatment, $n$ (%)</td>
<td>14/17 (82%)</td>
<td>14/16 (88%)</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>$98 \pm 28$</td>
<td>$106 \pm 20$</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>$63 \pm 22$</td>
<td>$72 \pm 14$</td>
</tr>
<tr>
<td>Anastomoses, median (IQR)</td>
<td>3 (3–4)</td>
<td>3 (3–5)</td>
</tr>
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</table>

Values are represented as means $\pm$ SD. BSA, body surface area; CPB, cardiopulmonary bypass; IQR, interquartile range.
flow index was higher in the pulsatile group (2.6 (2.5–2.9)) than in the nonpulsatile group (2.1 (1.7–2.5); \( P = 0.001 \)).

Data supplement. In a data supplement available with the online version of this manuscript, we show images of the microcirculation in two patients subjected to either nonpulsatile (left panels) or pulsatile flow (right panels) during CPB. The top panels represent microcirculatory perfusion upon the onset of CPB, showing a low perfused vessel density and cessation of blood flow. The bottom panels represent the perfusion of the sublingual mucosal microcirculation during ICU admission. It is clearly shown that the reduction in perfused vessel density and cessation of blood flow is continued during ICU admission in the nonpulsatile flow patient, whereas microcirculatory perfusion is restored to normal values after pulsatile flow.

Blood samples. Cardiac surgery with cardiopulmonary bypass induced an equal increase in plasma free hemoglobin in the nonpulsatile [from 0.12 ± 0.04 to 0.22 ± 0.15 mg/l (\( n = 15 \); \( P = 0.021 \)] and pulsatile group [from 0.10 ± 0.05 to 0.23 ± 0.12 mg/l (\( n = 14 \); \( P = 0.004 \)]. There were no differences in IL-6 [126.8 ± 78.7 pg/ml (\( n = 15 \)) vs. 122.0 ± 73.9 pg/ml (\( n = 12 \), \( P = 0.74 \)) or VEGF [7.8 ± 8.0 pg/ml (\( n = 14 \)) vs. 6.3 ± 8.7 pg/ml (\( n = 12 \), \( P = 0.92 \)] upon intensive care admission after nonpulsatile and pulsatile flow, respectively. TNF-\( \alpha \) levels tended to be elevated in the pulsatile flow group (21.3 ± 13.5 pg/ml; \( n = 13 \)) compared with the nonpulsatile flow group (12.6 ± 7.8 pg/ml (\( n = 15 \); \( P = 0.054 \)). Upon intensive care admission, there were no differences in leukocyte count [13.0 ± 4.9 × 10⁹/l (\( n = 16 \)) vs. 14.9 ± 7.8 × 10⁹/l (\( n = 16 \); \( P = 0.43 \)], C reactive protein [91.1 ± 57.1 mg/l (\( n = 15 \)) vs. 75.9 ± 44.3 mg/l (\( n = 14 \); \( P = 0.43 \)], or creatinine [82.4 ± 20.5 \( \mu \)mol/l (\( n = 17 \)) vs. 78.8 ± 19.0 \( \mu \)mol/l (\( n = 16 \); \( P = 0.61 \)] between nonpulsatile and pulsatile flow groups, respectively.

Clinical outcome. None of the subjects developed postoperative renal failure, myocardial infarction, or cerebrovascular accidents. In both nonpulsatile and pulsatile CPB groups, four patients developed de novo atrial fibrillation. There was no mortality in the first 30 days after surgery and all patients were discharged from the intensive care unit within 24 h after surgery.

DISCUSSION

Nonpulsatile flow during extracorporeal circulation was associated with sustained reduction in microcirculatory density and perfusion upon intensive care admission. In contrast, patients exposed to pulsatile flow showed a fast recovery of microcirculatory perfusion after weaning from cardiopulmonary bypass. This study is the first to demonstrate that pulsatile flow during extracorporeal circulation preserves microcirculatory perfusion as measured by sublingual SDF imaging of the microcirculation. Systemic hemodynamic parameters were not explanatory for the preservation of microcirculatory perfusion under pulsatile conditions. During cross-clamp time, pulsatile flow was associated with a slightly improved oxygen consump-

Table 2. Intra- and postoperative temperature, hemoglobin, and hematocrit

<table>
<thead>
<tr>
<th></th>
<th>Preop (T1)</th>
<th>AoX I (T3)</th>
<th>AoX II (T4)</th>
<th>ICU (T7)</th>
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<tbody>
<tr>
<td>Temperature, °C</td>
<td></td>
<td></td>
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<tr>
<td>NP</td>
<td>36.3 ± 0.5</td>
<td>35.3 ± 0.7*</td>
<td>35.4 ± 0.6*</td>
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<tr>
<td>P</td>
<td>36.2 ± 0.6</td>
<td>34.9 ± 0.7*</td>
<td>35.2 ± 0.6*</td>
<td></td>
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<tr>
<td>Hemoglobin, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>8.1 ± 0.6</td>
<td>5.4 ± 0.7*</td>
<td>5.6 ± 0.5*</td>
<td>7.0 ± 0.5*</td>
</tr>
<tr>
<td>P</td>
<td>7.9 ± 1.0</td>
<td>5.3 ± 0.9*</td>
<td>5.6 ± 0.9*</td>
<td>6.8 ± 0.8*</td>
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<tr>
<td>Hematocrit</td>
<td></td>
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</tr>
<tr>
<td>NP</td>
<td>0.39 ± 0.05</td>
<td>0.27 ± 0.04*</td>
<td>0.27 ± 0.03*</td>
<td>0.32 ± 0.03*</td>
</tr>
<tr>
<td>P</td>
<td>0.39 ± 0.05</td>
<td>0.26 ± 0.05*</td>
<td>0.28 ± 0.04*</td>
<td>0.32 ± 0.04*</td>
</tr>
</tbody>
</table>

Values represent means ± SD. NP = nonpulsatile (\( n = 17 \)); P = pulsatile (\( n = 16 \)). For definition of time points T1, T3, T4, and T7, see Materials and Methods. *\( P < 0.05 \) vs. T1, †\( P < 0.05 \) vs. T3.
tion and extraction rate, whereas nonpulsatile flow did not improve these parameters. Pulsatile and nonpulsatile CPB increased hemolysis equally. Despite better recovery of the microcirculation in the pulsatile group, no differences in clinical outcome parameters between pulsatile and nonpulsatile flow groups were found. However, the present study was not powered to detect differences between groups in clinical outcome, and we only included relatively healthy patients undergoing low-risk cardiac surgery. We hypothesize that the magnitude of our present findings may be enlarged in cardiosurgical procedures with a higher predicted mortality. To place our investigation in perspective, we showed that preservation of the physiological situation during extracorporeal circulation by means of pulsatile flow seems to markedly reduce microcirculatory recovery time, as it was previously shown that restoration of microvascular heterogeneity usually takes 6 h after surgery (8).

The beneficial effects of pulsatile flow on microcirculatory perfusion are in agreement with findings by others who showed that pulsatility reduced markers of endothelial damage and improved gastric mucosal oxygenation and tonometry (24, 28). Here we confirm these findings by direct measurements of microcirculatory perfusion. In contrast, Elbers et al. (10) recently showed that short-term pulsatile CPB was not beneficial for microcirculatory perfusion compared with nonpulsatile flow. This study focused especially on mechanical consequences of pulsatility rather than the effect of pulsatile flow on microcirculatory perfusion following surgery. Due to an average pulse pressure of 7 mmHg there was no true loss of pulsatility in their control group. Moreover, the crossover design of the study, which has earlier been criticized by Undar et al. (38), limits their conclusions and may further hinder comparison with our results.

An interesting study published by Onorati et al. (29) showed promising results for pulsatile flow in patients undergoing CABG surgery with intra-aortic balloon pump (IABP) support.

Fig. 3. Oxygen delivery index (DO$_2$, $A$), oxygen consumption index (VO$_2$, $B$), and oxygen extraction ratio (C) for nonpulsatile ($n = 17$) and pulsatile ($n = 16$) flow at the beginning (AoX start) and end (AoX end) of aortic cross-clamping. $\#P < 0.05$ vs. AoX start, paired t-test.

Fig. 4. Total small vessel density (A) and perfused small vessel density (B) for nonpulsatile (white circles; $n = 17$) and pulsatile (black squares; $n = 16$) cardiopulmonary bypass (CPB). After aortic cross-clamping (AoX) the perfused vessel density decreased in both groups, but only restored in the pulsatile group after removal of the aortic clamp ($P = 0.02$; pulsatile vs. nonpulsatile; repeated-measures ANOVA).
Postoperative renal function, liver function, lung function, and hemostasis and endothelial markers were all favorable in the pulsatile group. However, in agreement with our findings there were no differences in general inflammatory markers like IL-6 and TNF-α between nonpulsatile and pulsatile flow (29). Although the IABP-created pulse is different from the pulse generated by a centrifugal pump, the beneficial clinical results in IABP patients suggest that striving for pulsatility during CPB may be justified. Since IABP support is absent in the majority of CABG patients, pulsatility created in the extracorporeal system may provide an important alternative for this group of patients.

Preservation of endothelial function and reduction of inflammatory pathways are currently the most widely used concepts to explain the beneficial effects of pulsatile flow during CPB. It has indeed been shown that the absence of pulsatility is associated with capillary fall out, endothelial damage, endotoxin translocation and the production of cytokines, endothelin-1, lactate and catecholamines (2, 33, 41, 42). Interestingly, Sezai et al. (33) showed that the increased production of endothelin-1 with nonpulsatile flow starts no earlier than after weaning from cardiopulmonary bypass, simultaneously with impairment of microcirculatory recovery as shown in our investigation. However, we did not focus on vascular physiological mechanisms that may explain the beneficial effects of pulsatility. Future studies should therefore focus on the underlying mechanism of the beneficial effects of pulsatile flow during CPB. Most of the inflammatory markers that were determined in our investigation did not differ between both groups, and were therefore not explanatory for the observed differences in the restoration of microcirculatory flow.

Systemic hemodynamic changes were not of influence on microcirculatory perfusion after nonpulsatile or pulsatile CPB. This is in agreement with De Backer et al. (7), who earlier showed that microcirculatory perfusion is independent of hemodynamic parameters. Kindig et al. (20) showed that rats with chronic heart failure developed a decreased proportion of skeletal muscle vessels supporting red blood cell flux. This reduction in capillary perfusion is most probably attributed to an increased arteriolar tone, venous congestion, and reduced cardiac output. In contrast, reduced capillary perfusion during extracorporeal circulation is paralleled by an increase in cardiac output and reduction of systemic vascular resistance. From our findings it might be suggested that the acute onset of hemodilution, activation of inflammatory and coagulation pathways, and pulseless flow are more explanatory for the reduction in microcirculatory perfusion than changes in cardiac output. The findings of Kindig et al. (20) and our investigation demonstrate the diversity in physiological mechanisms that may lead to a change in capillary perfusion.

It has been shown that sepsis is associated with an increased heterogeneity of microcirculatory perfusion (11), which may subsequently lead to an impairment in oxygen extraction (12, 17). Moreover, heterogeneous perfusion of the microcirculation, reflected by a combination of blood flow cessation and hyperdynamic vessels, is deleterious for tissue oxygenation (15, 40). De Backer and coworkers (8) found that an increase in the heterogeneity of microcirculatory flow is also present during CPB. In line with this, our group (1) showed earlier that the onset of CPB is associated with decreased perfused capillary density, increased venular blood velocity, and increased microvascular hemoglobin oxygen saturation. Altogether, these findings suggest an increase in flow through a reduced number of capillaries, resulting in a decrease in erythrocyte oxygen offloading during CPB. In the present study we demonstrated that, after pulsatile CPB, perfused vessel density is recovered whereas oxygen consumption is improved during cross-clamp time. A recent study by Karaci et al. (19) also demonstrated that pulsatile flow is indeed associated with improvements in oxygen consumption and extraction ratio compared with nonpulsatile conditions. These and our findings hint toward the idea that pulsatile CPB is beneficial for recovering from microcirculatory heterogeneity, and consequently reduces the risk for a reduced oxygen extraction.

Finally, we showed that the differences in perfused vessel density between groups are the most pronounced after CPB and were undetectable during aortic cross-clamping. These findings might suggest that pulsatile flow has no direct effect on microcirculatory perfusion, but induces delayed physiological mechanisms that contribute to preservation of microcirculatory flow after surgery. The hypothesis that pulsatile energy is used to overcome a critical capillary closing pressure during CPB seems therefore unlikely (37, 43).

Increased hemolysis is a possible negative effect of pulsatile flow due to higher peak pressures in the extracorporeal circuit (30, 34). However, we did not find differences in post-bypass plasma free hemoglobin levels between the nonpulsatile and pulsatile groups. The concomitant negative effects of blood damage may reverse the beneficial effects of pulsatile cardiopulmonary bypass, which could be explanatory for the absent advantage of pulsatility as reported by some authors.

Our study is limited by the absent calculation of the energy equivalent pressure (EEP). Although EEP is regarded as the standard method for quantification of pulsatility we showed that complete absence of pulsatility during aortic-cross clamping is associated with disturbed microcirculatory perfusion compared with pulsatile CPB. In addition, we demonstrated that our pulsatile modality of the heart-lung machine was indeed associated with radial blood pressure waveforms with
an area under the curve of about 60% of the baseline systemic arterial blood pressure waveform.

Furthermore, one may argue whether the sublingual mucosa is representative for vital organs that may be affected by the deleterious effects of cardiopulmonary bypass on microcirculatory perfusion. Changes in microcirculatory flow in the sublingual mucosa are however well correlated with alterations in gastric and intestinal beds, as shown by Pco2 measurements, OPS and SDF-imaging, and colored-microsphere blood flow measurements (4, 6, 18, 23, 31, 39). In addition, the sublingual mucosa shares a common embryologic origin with the intestinal mucosa. Although extrapolation of the current data may be limited to splanchnic microcirculatory beds, these are of particular importance in maintenance of barrier integrity to prevent endotoxin translocation (41). Moreover, sublingual SDF and OPS-imaging studies have demonstrated that persistent sublingual microcirculatory disturbances are associated with poor outcome of critically ill patients (32, 36). Also, the sublingual microcirculation has been used in previous studies during cardiac surgery (1, 3, 8).

In conclusion, pulsatile flow by a centrifugal pump during aortic cross-clamp time is associated with preservation of microvascular perfusion in the early postoperative period, irrespective of systemic hemodynamics. While both nonpulsatile and pulsatile groups showed a marked decrease inperfused capillary density during cardiopulmonary bypass, microcirculatory perfusion only returned to preoperative baseline values in patients undergoing pulsatile cardiopulmonary bypass. Our findings were independent of systemic inflammatory blood parameters, whereas only pulsatile flow improved oxygen consumption during cross-clamping. These findings support the hypothesis that pulsatile flow may attenuate microcirculatory heterogeneity during extracorporeal circulation compared with nonpulsatile flow, although the underlying mechanism remains unknown. Although we found no differences in clinical outcome in our low-risk study population that underwent short-lasting, uncomplicated cardiosurgical procedures, further studies should elaborate whether preservation of microcirculatory perfusion in the early postoperative period due to intraoperative pulsatile flow is additionally associated with improved outcome in patients undergoing more complicated cardiac surgery.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


