The microcirculatory response during cardiac surgery

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Red blood cell transfusion compared with gelatin solution and no infusion after cardiac surgery: effect on microvascular perfusion, vascular density, hemoglobin and oxygen saturation

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Abstract

**Background:** After cardiac surgery, red blood cell (RBC) transfusion may improve systemic hemodynamics and thereby microvascular blood flow and O\(_2\) delivery.

**Study design and methods:** In a non-randomized prospective observational study on post cardiac surgery patients, systemic hemodynamics and microvascular blood flow, vascular density (sidestream dark-field imaging), hemoglobin content and saturation (reflectance spectrophotometry) were measured prior to and 1 h after start of transfusion of 1-2 units of leucodepleted RBC concentrates (270±203 mL), 500 mL of gelatin solution or control (no infusion), when patients were considered clinically hypovolemic with (RBC group n=12) or without (gelatin group, n=14) anemia (hemoglobin [Hb] <10 g/dL) or not (n=13), respectively.

**Results:** Systemic hemoglobin was lower and increased in the RBC transfusion but not in gelatin and controls groups. There were no differences in changes in systemic O\(_2\) delivery, O\(_2\) uptake and extraction between groups. RBC transfusion, as compared with gelatin or control, increased medium-sized vascular density, Hb content and saturation in the microcirculation, while blood flow remained unchanged. Changes of microvascular Hb and saturation paralleled changes in systemic Hb.

**Conclusion:** The data argue in favor of efficacy of RBC transfusion after cardiac surgery. RBC transfusion increases systemic Hb and this in turn increases medium-sized vascular density and O\(_2\) delivery in the sublingual microcirculation, independently of systemic hemodynamics and volume status.

**Keywords:** blood transfusion, microcirculation, sidestream dark-field imaging, reflectance spectrophotometry, post-cardiac surgery
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Introduction

Postoperative red blood cell (RBC) transfusions and colloid infusions are commonly used to treat anemia, hypovolemia or both after cardiac surgery. The aim is improvement of tissue oxygenation and thereby, presumably, prevention of postoperative complications, which may relate, in part, to tissue hypoxygenation.\(^1\) On the other hand, studies in cardiac surgery patients have shown an association between perioperative or postoperative RBC transfusions, even when leucodepleted, and a poor outcome.\(^3\)\(^-\)\(^7\)

Microvascular effects of RBC transfusions have been investigated in septic and critically ill patients in general.\(^8\)\(^,\)\(^9\) They may only improve sublingual microvascular perfusion, as detected by orthogonal polarization spectroscopy imaging, in a subpopulation of patients with diminished perfusion at baseline. In another study, tissue oxygenation was unaltered by RBC transfusion as measured by near-infrared spectroscopy (NIRS), unless low at baseline.\(^9\) There is only one study to suggest that RBC transfusion may recruit a diminished microcirculation during cardiac surgery,\(^4\) which may otherwise gradually return to normal after transfer to the intensive care unit (ICU).\(^2\) On the other hand, long stored and stiff RBC's may impair microvascular blood flow and tissue oxygenation, at least in experimental studies,\(^10\)\(^-\)\(^13\) so that the efficacy of RBC transfusions, even in terms of global hemodynamics, remains controversial.\(^1\)\(^,\)\(^14\) Indeed, hemodynamic effects could relate to the volume infused and the associated increase in viscosity rather than to the O\(_2\)-carrying hemoglobin itself. Finally, the microvascular effects of infusion of asanguineous gelatin solution are unknown, whereas potential benefits of synthetic colloids in fluid resuscitation after cardiac surgery, for instance, in terms of systemic hemodynamics and outcome are well studied, although remaining highly controversial.\(^15\)

In the current study, we hypothesized that transfusion of normally stored RBC, increases microvascular O\(_2\) delivery by increasing the systemic hemoglobin (Hb) concentration independently of a volume effect, after cardiac surgery. We therefore compared the effects of RBC transfusion, gelatin infusion, in clinically hypovolemic patients with or without concomitant anemia, respectively, and no infusion in patients without anemic hypovolemia, on systemic and microcirculatory hemodynamics and O\(_2\) delivery, by sidestream dark-field (SDF) imaging for microcirculatory blood flow and functional vascular density, and by reflectance spectrophotometry for Hb content and saturation.
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Materials and methods

Patients

This study was a non-randomized and non-blinded study, approved by the Human Subjects Committee of the Free University Medical Center (Amsterdam, the Netherlands). Written informed consent was obtained from all patients prior to surgery. Patients were studied within three hours after cardiac surgery while still sedated and mechanically ventilated. Patients fulfilled the following inclusion criteria: age >18 or <80 years, pulmonary artery and radial artery catheters in place, the first RBC transfusion or gelatin infusion as part of routine clinical management, a temperature >35 °C, preoperatively obtained informed consent and not severely hemodynamically compromised with dopamine <5 µg/kg/min and systolic blood pressure >80 mm Hg. Exclusion criteria were preterminal illness with <24 h life expectancy, hypersensitivity to gelatins and bleeding from drains exceeding 100 mL/h after surgery. The study population consisted of 39 consecutive patients who underwent cardiac surgery and were admitted to the ICU. After admission, clinically hypovolemic and anemic (Hb <10 g/dL) or clinically hypovolemic and non-anemic patients, or non-hypovolemic, non-anemic patients were included in the study and treated with either leucodepleted RBC concentrate (1-2 units, ie 200-540 mL) with known storage time (n=12), 500 mL of gelatin (Gelofusine®, gelatin 40 g/L, B. Braun Melsungen AG, Germany, in 154/120 mmol/L NaCl 0.9%) (n=14), or no infusion (n=13), respectively, at the discretion of the treating physician, deciding on the routine care of cardiac surgery patients according to institutional guidelines. The latter include maintaining Hb at about 10 g/dL and fluid loading and infusion of dopamine in case of hypotension. Clinical hypovolemia was defined by, at least one of the following but not limited to, systolic arterial pressure <110 mm Hg, a central venous pressure <9 mm Hg, a mixed venous O₂ saturation <60%, oligo-anuria and need for vasopressor support.

Protocol

Patients were transferred to the ICU directly after surgery and all measurements were conducted within three hours after admission. The study was started as soon as inclusion criteria were met and RBC’s, gelatin or nothing was judged needed by treating physicians. Demographics were recorded and baseline measurements and blood samples were taken over 15-30 min. Ventilatory settings and vasopressor/inotropic/sedative/analgesic drug doses were unaltered and recorded, as well as durations of mechanical ventilation and stay in the ICU. Prior to (T=0) and 1 hour after starting (T=1) transfusion of 1-2 units of RBC concentrate in
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15-30 min, 500 mL of gelatin solution in 15 min, or baseline measurements in the no infusion group, the following measurements were done and samples taken.

Hemodynamic and laboratory measurements
Systemic hemodynamic monitoring included continuous arterial blood pressure and intermittent cardiac output measurements using a radial artery and pulmonary artery catheter, respectively. We measured body temperature, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), as well as arterial and mixed venous blood gases. The HR was taken from the continuously recorded electrocardiogram. Pressures were measured with patients in the supine position after calibration, zeroing to atmospheric pressure and, for PAOP, after proper wedging, at the midchest level (Tramscope®, Marquette, GE, Milwaukee, Wisc., USA) and end-expiration. For the average of 3 measurements of cardiac output, the bolus thermodilution method was used. The measurements involve a central venous injection of 10 mL of an ice-cold 5% glucose solution. Triplicate values taken irrespective of the ventilatory cycle were averaged. In 5 mL aliquots of heparinized blood, we determined Hb (Sysmex SE-9000, Sysmex Corporation, Kobe, Japan), partial O\textsubscript{2} pressure, saturation and O\textsubscript{2} content (Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA). O\textsubscript{2} delivery (DO\textsubscript{2}), O\textsubscript{2} consumption (VO\textsubscript{2}) and O\textsubscript{2} extraction ratio (O\textsubscript{2}ER) were calculated using standard formulas.

Imaging and analysis of the sublingual mucosal microcirculation
Imaging of the sublingual mucosal microcirculation was performed using sidestream dark-field (SDF) imaging (MicroScan; Micro Vision Medical, Amsterdam, Netherlands) which is a noninvasive handheld videomicroscopy whose light guide is placed on organ surfaces for direct microscopic observation of the microcirculation.\textsuperscript{3,16} Three different regions of the sublingual microcirculation were recorded and used for off-line computer analysis by investigators blinded for the infusions. Averaged values are reported. Dedicated automated microvascular analysis software was used to quantify functional density of capillaries and venules. Quantification of blood flow was classified as follows: 0=no flow, 1=intermittent flow 2=slugging flow and 3=continuous flow, and expressed as microvascular flow index (MFI). Vascular densities (mm/mm\textsuperscript{2}) of small (<25 um, probably mainly capillaries) and medium-sized (>25 um, probably mainly venules) vessels were also assessed.
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Sublingual microvascular Hb O\textsubscript{2} saturation (HbSO\textsubscript{2})

An optical probe (O2C; Lea Medizintechnik, Giessen, Germany) containing reflectance spectrophotometry was used by placement on the sublingual tissue to measure averaged (mainly venular) microvascular Hb concentration (au, arbitrary units) and HbSO\textsubscript{2} and was previously used in cardiac surgery.\textsuperscript{3,17} After removal of saliva by gauze, the optical fiber probe was placed and fixed under the tongue for continuous measurement in one sublingual location. The tissue was illuminated by a visible white light (500-630 nm), and the spectrum of reflected light was measured. Analysis of this spectrum provides the SO\textsubscript{2} of the available erythrocytes. A one-minute tracing of this spectrum was averaged for HbSO\textsubscript{2} values. An increase in HbSO\textsubscript{2} indicates improved microvascular O\textsubscript{2} delivery.

Statistical analysis

Since we could not estimate the magnitude of the expected changes, there was no formal power calculation. We included patients until at least 12 were reached per group. Variables were normally distributed, according to results by Kolmogorov-Smirnov testing (P>0.05). Because of relatively small numbers, we nevertheless used non-parametric tests (Wilcoxon signed rank test) for changes in the whole group and (Kruskal-Wallis ANOVA) for differences between RBC, gelatin and no infusion groups in values at baseline and in changes. If the Kruskal-Wallis test indicated significance, we explored with the Mann-Whitney U test whether changes in the RBC differed from those in the gelatin group and whether the gelatin group differed from control. The X\textsuperscript{2} test was used to evaluate differences in proportions. The κ statistic was used to evaluate concordance, independent of group differences in changes, between changes in the systemic and the microcirculation. A P<0.05 was considered statistically significant. Values are summarized as mean ± standard deviations (SD) or numbers, where appropriate.

Results

Patients

Patient demographics, comorbidity, and type of cardiac surgery were comparable among groups (Table 1). Ten of 39 patients had undergone grafting without cardiopulmonary bypass. There were relatively more females among patients receiving RBC transfusions. All patients had an uneventful course and were discharged from the ICU within 24 h.
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Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>RBC</th>
<th>Gelatin</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=12</td>
<td>n=14</td>
<td>n=13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>67 ± 9</td>
<td>67 ± 10</td>
<td>65 ± 12</td>
<td>0.86</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/5</td>
<td>10/4</td>
<td>13/0</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 4</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>0.57</td>
</tr>
<tr>
<td>EuroSCORE (additive)</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
<td>5 ± 3</td>
<td>0.73</td>
</tr>
<tr>
<td>Length of stay ICU, hr</td>
<td>29 ± 27</td>
<td>26 ± 9</td>
<td>19 ± 6</td>
<td>0.09</td>
</tr>
<tr>
<td>Mechanical ventilation, hr</td>
<td>12 ± 7</td>
<td>13 ± 12</td>
<td>9 ± 5</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Comorbidity

- Diabetes mellitus: 4/3/1, P=0.56
- Hypertension: 2/5/6, P=0.15
- COPD: 1/0/1, P=0.55
- Current smoking: 1/2/4, P=0.31

Surgery

- CABG: 6/8/6, P=0.26
- CABG + valve surgery: 3/0/4
- Valve surgery: 3/6/3
- CPB time, min: 142 ± 57, 102 ± 32, 137 ± 54, P=0.21
- Aortic clamp time, min: 93 ± 50, 70 ± 32, 103 ± 52, P=0.51

Treatment

- Infusion volume, mL: 270 ± 203, 500, -
- RBC storage time, days: 18 ± 6, -
- Dopamine, μg/kg/min: 1.6 ± 1.6, 1.9 ± 1.4*, 0.6 ± 0.8, P=0.07

Mean±SD or number, where appropriate. RBC= red blood cell; BMI= body mass index; COPD= chronic obstructive pulmonary disease; CABG= coronary artery bypass grafting; CPB= cardiopulmonary bypass; na= not applicable.
*P=0.02 vs Control.
### Table 2. Systemic cardiorespiratory variables.

<table>
<thead>
<tr>
<th></th>
<th>RBC</th>
<th>Gelatin</th>
<th>Control</th>
<th>P (Kruskal-Wallis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T=0</td>
<td>T=1</td>
<td>T=0</td>
<td>T=1</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.2 ± 0.4</td>
<td>36.2 ± 0.5</td>
<td>35.7 ± 1.9</td>
<td>36.1 ± 0.3</td>
</tr>
<tr>
<td>Heart rate, bpm¹</td>
<td>76 ± 16</td>
<td>74 ± 25</td>
<td>84 ± 9</td>
<td>77 ± 10</td>
</tr>
<tr>
<td>MAP, mmHg²</td>
<td>68 ± 5</td>
<td>79 ± 10</td>
<td>66 ± 10</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.3 ± 1.3</td>
<td>3.9 ± 0.9*</td>
<td>5.8 ± 2.2</td>
<td>6.2 ± 2.3†</td>
</tr>
<tr>
<td>CVP, mmHg³</td>
<td>5 ± 2</td>
<td>7 ± 4</td>
<td>5 ± 2</td>
<td>6 ± 2†</td>
</tr>
<tr>
<td>PAOP, mmHg</td>
<td>13 ± 5</td>
<td>13 ± 7</td>
<td>10 ± 4</td>
<td>10 ± 4</td>
</tr>
<tr>
<td><strong>O₂ transport</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PₐO₂, mmHg⁴</td>
<td>106 ± 43</td>
<td>117 ± 27</td>
<td>130 ± 42</td>
<td>129 ± 31</td>
</tr>
<tr>
<td>PᵥO₂, mmHg</td>
<td>36 ± 4</td>
<td>35 ± 5</td>
<td>37 ± 5</td>
<td>39 ± 7</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>8.8 ± 0.5</td>
<td>9.8 ± 0.6**</td>
<td>10.7 ± 1.1</td>
<td>10.2 ± 1.3</td>
</tr>
<tr>
<td>Sₒ₂₂, %⁵</td>
<td>60 ± 4</td>
<td>64 ± 4</td>
<td>61 ± 4</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>DO₂, mL/min</td>
<td>520 ± 145</td>
<td>530 ± 105</td>
<td>684 ± 120</td>
<td>774 ± 228</td>
</tr>
<tr>
<td>VO₂, mL/min</td>
<td>202 ± 57</td>
<td>189 ± 41</td>
<td>265 ± 59</td>
<td>281 ± 129</td>
</tr>
<tr>
<td>O₂ER, %⁶</td>
<td>39 ± 4</td>
<td>36 ± 4</td>
<td>39 ± 4</td>
<td>36 ± 5</td>
</tr>
<tr>
<td><strong>Respiratory variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FᵢO₂, %</td>
<td>46 ± 8</td>
<td>44 ± 9</td>
<td>44 ± 7</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>Vₜ, mL</td>
<td>476 ± 57</td>
<td>436 ± 67</td>
<td>477 ± 57</td>
<td>470 ± 67</td>
</tr>
<tr>
<td>PEEP, cmH₂O</td>
<td>6 ± 2</td>
<td>7 ± 2</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
</tr>
</tbody>
</table>

Mean ± SD; T=0 at baseline and T=1, 1 h after start of transfusion, infusion or first measurements. RBC= red blood cell transfusion; MAP= mean arterial pressure; CVP= central venous pressure; PAOP= pulmonary artery occlusion pressure; PₐO₂= arterial partial O₂ pressure; PᵥO₂= mixed venous PO₂; Hb= hemoglobin; Sₒ₂₂= mixed venous O₂ saturation; DO₂= O₂ delivery; VO₂= O₂ consumption; O₂ER= O₂ extraction ratio; FᵢO₂= inspiratory O₂ fraction; Vₜ= tidal volume; PEEP= positive end-expiratory pressure. ¹P=0.02, ²P=0.008, ³P=0.04, ⁴P=0.04, ⁵P=0.006, ⁶P=0.005 for change in whole group; *P=0.006, **P<0.001 for change vs Gelatin; †P=0.01, ‡P=0.02 for change vs Control.
Table 3. Microvascular hemodynamics.

<table>
<thead>
<tr>
<th></th>
<th>RBC n=12</th>
<th>Gelatin n=14</th>
<th>Control n=13</th>
<th>P (Kruskal-Wallis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T=0</td>
<td>T=1</td>
<td>T=0</td>
<td>T=1</td>
</tr>
<tr>
<td>Flow index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>small</td>
<td>2.2 ± 0.8</td>
<td>2.5 ± 0.4</td>
<td>2.3 ± 0.7</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>medium</td>
<td>2.7 ± 0.3</td>
<td>2.8 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>Vascular density, mm/mm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>small</td>
<td>12.5 ± 2.0</td>
<td>12.8 ± 2.7</td>
<td>13.0 ± 3.4</td>
<td>14.2 ± 4.9</td>
</tr>
<tr>
<td>medium</td>
<td>0.5 ± 0.5</td>
<td>0.7 ± 0.4*</td>
<td>0.8 ± 0.6</td>
<td>0.6 ± 0.4</td>
</tr>
<tr>
<td>Hb, au</td>
<td>72 ± 11</td>
<td>78 ± 10**‡</td>
<td>77 ± 9</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>HbSO₂, %</td>
<td>74 ± 12</td>
<td>76 ± 12***‡</td>
<td>77 ± 7</td>
<td>75 ± 7</td>
</tr>
</tbody>
</table>

Mean ± SD; T=0 at baseline and T=1, 1 h after start of transfusion, infusion or first measurements. RBC= red blood cell transfusion; Hb= hemoglobin concentration; HbSO₂= hemoglobin O₂ saturation; au= arbitrary units. *P<0.01, **P<0.001, ***P<0.01 for change vs Gelatin and †P<0.008 and ‡P<0.016 for change vs Control.
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Figure 1. The change of relative microvascular hemoglobin (Hb) concentrations of the sublingual microcirculation as function of the change of systemic Hb concentration in cardiac surgery patients after postoperative transfusion of red blood cells (RBC, black dots) or infusion of gelatin (open dots) and in control patients (triangles). It is shown that changes in microcirculatory Hb were directionally similar to those in systemic Hb ($\kappa = 0.29$, $P=0.01$), so that RBC transfusion (versus gelatin and no infusion) increased both. au: arbitrary units.

Systemic hemodynamics
Body temperature and PAOP remained unchanged in RBC, gelatin or control groups (Table 2). Cardiac output, while lower at baseline, decreased in the RBC but not in the other groups. The rise in cardiac output and CVP in the gelatin was greater than in the control group, whereas baseline values were similar. While lower at baseline, systemic Hb increased in the RBC group, whereas it decreased in the gelatin and control groups. $S_O^2$ rose and $O_2$ER fell in the whole group. There were no differences in changes in $DO_2$, $VO_2$ and $O_2$ER between the groups, while baseline $DO_2$ and $VO_2$ were lower in the RBC than the other groups. All patients had arterial $O_2$ saturations of 99%, whereas baseline $V_t$ was highest in the control group.

Microvascular hemodynamics (Table 3)
Baseline variables were similar among groups and did not differ among patients after off- or on-pump surgery (data not shown). The MFI and the density of small vessels did not change.
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![Graph showing changes in microvascular hemoglobin (Hb) concentrations.](image)

**Figure 2.** The relation between the changes in microvascular sublingual hemoglobin (Hb) O$_2$ saturations and those in systemic Hb concentrations in cardiac surgery patients after postoperative transfusion of red blood cells (RBC, black dots) or infusion of gelatin (open dots) and in control patients (triangle). It is shown that changes in microcirculatory Hb O$_2$ saturation were directionally similar to those in systemic Hb ($\kappa=0.22$, $P=0.04$), so that RBC transfusion (versus gelatin and no infusion) increased both. au: arbitrary units.

in either group. However, the density of medium-sized vessels increased in the RBC as compared with the gelatin and control groups. The microvascular Hb concentration and HbSO$_2$ also increased in the RBC group. Effects of gelatin solution did not differ from control.

**κ statistics**

As shown in Figure 1, the direction of change in microvascular Hb concentration was similar to the change in systemic Hb concentration, so that RBC transfusion, in contrast to gelatin or no infusion, increased both. This was also associated with a rise in microvascular HbSO$_2$ (Fig. 2). The change in medium-sized vascular density paralleled the change in systemic Hb ($\kappa=0.23$, $P=0.05$). Storage time of RBC’s did not relate to any of these microvascular parameters.
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Discussion

The main findings of this study are that, after cardiac surgery, RBC transfusion improves systemic and microvascular Hb and HbSO2 at unchanged MFI, thus increasing microvascular O2 delivery, independently of systemic hemodynamics and oxygenation. This is associated with recruitment of medium-sized vessels.

Although the rises in S,O2 and falls in O2ER indicate a higher O2 supply-demand ratio, changes did not differ between the groups. Infusion of gelatin solution increased cardiac output but not DO2, because of concomitant hemodilution, as described elsewhere.18 Indeed, infusion was associated with an unchanged MFI and O2 delivery in the microcirculation. This disagrees with the literature on hemorrhagic shock in pigs19 but may help to explain the lack of patient-centered benefits of resuscitation with synthetic colloids in critically ill hypovolemic patients, even when improving systemic hemodynamics.15

Our study agrees with studies in animals10,11 and in humans during cardiac surgery,4 that RBC transfusion increases sublingual microvascular density and HbSO2 but not the MFI. The increase in microvascular Hb and (venular) HbSO2 at unchanged MFI otherwise implies a rise in microvascular O2 delivery rather than arteriovenous shunting, even though microvascular was higher than S,O2. Systemic DO2 did not increase with RBC transfusion because the rise in Hb was offset by a fall in cardiac output, at unchanged tissue requirements (VO2), as commonly observed and attributable to a rise in blood viscosity and systemic vascular resistance.1,14 However, RBC transfusion may increase systemic DO2 (at unchanged O2 uptake) and capillary perfusion when low at the start in critically ill, septic patients.8 In the Créteur et al. study,9 NIRS-derived tissue O2 variables did not increase by RBC transfusion in septic and non-septic patients, except, again, when low at the start.9 In contrast to similar effects on systemic oxygenation, RBC transfusion thus had greater effects than gelatin infusion on the microcirculation in our study. Therefore, the results suggest greater effect on tissue vascular density and O2 delivery by Hb than by systemic hemodynamics and volume status. This agrees with experimental conditions, at least when Hb O2 affinity is normal.10,12,20,21 Apparently, the medium-sized vessels in the microcirculation, most likely venules, accommodated for the increased numbers of RBC’s by their capacitance function. Future studies are necessary on the patient-centered, clinical correlates of these findings. They nevertheless suggest that potential detrimental sequelae of, often non-leucodepleted, RBC transfusions after cardiac surgery, may be attributable to adverse effects that do not relate to
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the microcirculation, unless storage times are unduly prolonged.\textsuperscript{1-4,10,11} Indeed, storage-induced stiffening of RBC may compromise rather than increase microvascular variables.\textsuperscript{1,10-13} Otherwise, our RBC group may be too small, the storage time too short, or both, to reveal an effect of RBC storage on microvascular parameters, as noted before.\textsuperscript{8,9}

Previously, we investigated the sublingual microcirculation during normovolemic hemodilution, following start of extracorporeal pump perfusion in coronary artery surgery patients, and found an increased microvascular MFI and HbSO\textsubscript{2}, and a reduction of capillary density.\textsuperscript{3} That our current observations on RBC transfusions are not entirely opposite to those in our previous study may be caused, in part, by concomitant anesthesia and a rise (rather than a fall) in cardiac output in the latter. Also, microvascular O\textsubscript{2} delivery may be bell-shaped according to the Hb determining blood viscosity. Finally, our current patients in the RBC or gelatin group were considered clinically hypovolemic and indeed tended to receive higher dopamine doses, while the patients in the gelatin group were, on the average, fluid responsive, ie increased their cardiac output. Nevertheless, baseline microcirculatory variables in the intervention groups did not differ from the control (no infusion) group, suggesting relative insensitivity of the microcirculation to (the degree of) hypovolemia and anemia in our study, but we cannot exclude that hypovolemia had partly offset an effect of anemia. Otherwise, it may take 24 h for changes during pump perfusion to gradually normalize in the ICU.\textsuperscript{2-4} We did not observe an effect of pump vs off pump perfusion, described before.\textsuperscript{2}

Apart from relatively small groups, limitations of the current study include a non-randomized design, since randomization for RBC transfusion would be hardly feasible, even though indications for transfusion after cardiac surgery are relatively poorly established.\textsuperscript{14} We therefore studied effects of RBC transfusion according to our clinical practice in a ‘real life’ situation. The study carries the advantage of a gelatin infusion group to control for volume status. Baseline hemodynamics did not differ between groups except for lower Hb, cardiac output and O\textsubscript{2} variables prior to RBC transfusion, as may be expected. This may have partly confounded our results.

In conclusion, this study supports the efficacy of RBC transfusion after cardiac surgery, so that a rise in systemic Hb increases medium-sized vascular density and O\textsubscript{2} delivery in the sublingual microcirculation, independently of systemic hemodynamics and volume status. The clinical implications need further study.
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