Blood transfusions recruit the microcirculation during cardiac surgery

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BACKGROUND: Perioperative red blood cell transfusions are commonly used in patients undergoing cardiac surgery to correct anemia caused by blood loss and hemodilution associated with cardiopulmonary bypass circulation. The aim of this investigation was to test the hypothesis that blood transfusion has beneficial effects on sublingual microcirculatory density, perfusion, and oxygenation. To this end, sidestream dark field (SDF) imaging and spectrophotometry were applied sublingually before and after blood transfusion during cardiac surgery.

STUDY DESIGN AND METHODS: Twenty-four adult patients undergoing on-pump cardiac surgery, including coronary artery bypass grafting, cardiac-valve surgery, or a combination of these two procedures, were included consecutively in this prospective, observational study. Sublingual microcirculatory density and perfusion were assessed using SDF imaging in 12 patients (Group A). Sublingual reflectance spectrophotometry was applied in 12 patients (Group B) to monitor microcirculatory oxygenation and hemoglobin (Hb) concentration.

RESULTS: Blood transfusion caused an increase in systemic Hb concentration ($p < 0.01$) and hematocrit ($p < 0.01$). At the microcirculatory level, blood transfusion resulted in increased microcirculatory density (from 10.5 ± 1.2 to 12.9 ± 1.2 mm capillary/mm^2 tissue, $p < 0.01$) as shown using SDF imaging. In concert with the SDF measurements, spectrophotometry showed that microcirculatory Hb content increased from 61.4 ± 5.9 to 70.0 ± 4.7 AU ($p < 0.01$) and that microcirculatory Hb oxygen saturation increased from $65.6 \pm 8.3\%$ to $68.6 \pm 8.4\%$ ($p = 0.06$).

CONCLUSION: In this study we have shown that blood transfusion: 1) improves the systemic circulation and oxygen-carrying capacity, 2) improves sublingual microcirculatory density but not perfusion velocity, and 3) improves microcirculatory oxygen saturation.

Perioperative red blood cell (RBC) transfusions are commonly used in patients undergoing cardiac surgery to correct anemia caused by blood loss and hemodilution associated with cardiopulmonary bypass (CPB) circulation and anesthesiologic procedures. Although RBC transfusions seem required to correct and/or prevent anemia, several studies have shown that it might have adverse effects on patient outcome in terms of morbidity (e.g., renal failure),[1-3] mortality,[4,5] postoperative infectious complications,[6,7] and increased hospital length of stay.[8] However, while these endpoints can be used to evaluate the complications that occur after surgical procedures, they are not sensitive markers of tissue hypoxia, nor can they be used to monitor the specific effects of blood transfusions. Furthermore, the adverse effects previously associated with blood transfusion have mostly been demonstrated in clinical studies performed with nonleukoreduced blood. Two meta-analyses of leukoreduced versus nonleukoreduced blood transfusions demonstrated that prestorage leukoreduction was associated with a significant improvement in outcome in cardiac surgery patients.[9,10]

Ultimately, the goal of RBC transfusions is to improve oxygen delivery to parenchymal cells by increasing the presence of RBCs at the microcirculatory level. This issue, however, has been addressed in very few clinical studies.

ABBREVIATIONS: CPB = cardiopulmonary bypass; DVL = detected vessel length; FCD = functional capillary density; ICU(s) = intensive care unit(s); MFI = microvascular flow index; SDF = sidestream dark field.

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Moreover, the few clinical studies that did investigate the effects of blood transfusions on the microcirculation were performed in septic patients.[11,12] In a study employing orthogonal polarization spectral imaging (technology similar to sidestream dark field [SDF] imaging) for investigating the effects of RBC transfusions on microcirculatory perfusion in severely septic patients, the authors demonstrated that RBC transfusions improved the sublingual microcirculatory perfusion in a subpopulation of patients.[11] In another study, near-infrared spectroscopy has been applied to measure tissue microcirculatory oxygen saturation changes during RBC transfusion in septic patients. The authors found that tissue oxygenation was unaltered by RBC transfusion.[12] However, while these studies were performed to clarify the effects of RBC transfusion at microcirculatory level, they cannot distinguish between the effects of sepsis and the effects of RBC transfusions. In sepsis, hemorheologic alterations and damaged host microcirculation (e.g., endothelium and glycocalyx) could diminish the efficacy of RBC transfusions to correct anemia at the microcirculatory level. Hence, the effects of RBC transfusions in a condition of (relatively) healthy host microcirculation remain to be investigated.

In this study we tested the hypothesis that leukoreduced RBC transfusions improve microcirculatory density, perfusion, and oxygenation in hosts with (relatively) healthy microcirculation, that is, in patients undergoing CPB-assisted cardiac surgery. To this end, sublingual microcirculatory density and perfusion were assessed using SDF imaging and sublingual reflectance spectrophotometry was applied to monitor microcirculatory oxygenation and hemoglobin (Hb) concentration.

MATERIALS AND METHODS

The study protocol was approved by local medical ethics committee of Academic Medical Center, Amsterdam, and written informed consent was obtained from all studied subjects. The study was done in compliance with the principles established in the Helsinki Declaration.

Patients

Twenty-four adult patients undergoing on-pump cardiac surgery, including coronary artery bypass grafting, cardiac-valve surgery, or a combination of these two procedures, that received allogenic blood transfusions during surgery were included consecutively in this prospective, observational study. Exclusion criteria were age below 18 years, withdrawal of consent, pregnancy, and recent oral surgery.

Sublingual microcirculatory density and perfusion were assessed using SDF imaging (Microscan, Microvision Medical, Amsterdam, the Netherlands) in 12 patients (Group A). Sublingual reflectance spectrophotometry (Oxygen-To-See, O2C, LEA medizintechnik, Gießen, Germany) was applied in 12 patients (Group B) to monitor oxygen availability and Hb concentration. The measurements were performed before and 30 minutes after blood transfusion during on-pump cardiac surgery to observe the optimum changes after RBC transfusions. These time points were chosen based on our results in earlier pilot studies. Sublingual SDF and O2C measurements were performed in separate groups as the techniques could not be applied simultaneously due to light interference between methods.

Anesthetics and CPB protocol

All patients received a standardized anesthesia including scopolamine, fentanyl, pancuronium, etomidate, and propofol as well as full heparinization (3 mg/kg) just before the cannulation to achieve a target activated clotting time of more than 400 seconds before CPB. The extracorporeal circuit was connected by use of ascending aortic cannulation and venous cannulation of the right atrium. The aortic cross-clamp was placed within minutes after onset of CPB resulting in nonpulsatile blood flow fully generated by a roller-pump (Sarns 9000 perfusion system, 3M Health Care Group, Dearborn, MI) at 10 minutes. The flow rates were maintained at 2.4 L/m^2/min. The oxygenator priming contained 200 mL of trasylol, 1100 mL of Ringer's solution, 300 mL of albumin, 200 mL of mannitol, and 50 mL of sodium bicarbonate adding up to a total standard mix of 1850 mL. All patients were cooled to systemic mild hypothermia (28-32°C) and oxygenated with a membrane oxygenator (COBE Cardiovascular, Inc., Lakewood, CO). The patients were fully rewarmed to 37°C before the end of the operation. Standard monitoring methods including electrocardiography, radial artery line, central venous catheter (Schwanz-Ganz), two peripheral venous catheters, urinary catheter, and rectal and nasal temperature measurement were used in all patients.

SDF imaging

Sublingual microcirculatory density and perfusion were perioperatively monitored using SDF imaging. SDF imaging is an optical modality that is incorporated in a hand-held microscope with a light guide at the end of which is a magnifying lens. In SDF imaging, illumination is provided by surrounding a central light guide with concentrically placed green light-emitting diodes to provide SDF illumination. The lens system in the core of the light guide is optically isolated from the illuminating outer ring preventing the microcirculatory image from contamination by tissue surface reflections. Light from the illuminating outer ring of the SDF probe, which penetrates the tissue, illuminates the tissue-embedded microcirculation

by scattering. This leads to images where RBCs are depicted as dark moving globules against a bright background. To improve the imaging of moving structures, such as flowing RBCs, the light-emitting diodes provide pulsed illumination in synchrony with the CCD frame rate. This stroboscopic imaging (partially) prevents smearing of moving features, such as flowing RBCs, and motion-induced blurring of capillaries due to the short illumination intervals.[13]

In this study, in compliance with recently published consensus report on the performance and evaluation of microcirculation using SDF imaging,[14] the SDF probe, covered by a sterile disposable cap, was placed on sublingual tissue surface avoiding pressure artifacts[15] before and 30 minutes after RBC transfusion. Five different sublingual microcirculatory sites (>20 sec/site) were recorded at both time points with adequate focus and contrast. The obtained images were stored on DVI tape and were later captured in 5- to 10-second stable (i.e., with minimal image drift) video clips in DV-AVI file format. SDF images were analyzed for functional capillary density (FCD; (mm capillary/mm^2 tissue) and detected vessel length (DVL; mm) using a computer software package (Automated Vascular Analysis Software, Microvision Medical BV, Amsterdam, the Netherlands). Additionally, microvascular flow index (MFI; AU), providing an index for microcirculatory blood flow velocity, was analyzed semiquantitatively in small- (diameter < 25 μm) and medium-sized vessels (25 μm < diameter < 100 μm) as described previously.[16]

Spectrophotometry

Sublingual microcirculatory oxygen saturation and Hb content were measured using spectrophotometry (O2C).[17] For spectrophotometry, tissue was illuminated with visible (white) light and the spectrum of the backscattered light was analyzed to calculate the tissue optical absorption spectrum. The O2C device determines the Hb oxygen saturation based on the differentiating absorption spectra of oxygenated and deoxygenated Hb. Oxygenated Hb has two absorption peaks in the visible spectrum, centered on 542 and 577 nm, and deoxygenated Hb has one absorption peak, centered on 556 nm. Hence, by scaling the measured absorption spectrum between the known absorption spectra of oxygenated and deoxygenated Hb, the Hb oxygen saturation can be determined. The total optical absorption is used to reflect the tissue Hb content.

The measurement depth of the O2C device was estimated as half the spacing between the illumination fiber and the detection fiber. For the probe applied in this study, this was approximately 1 to 2 mm. Due to the relatively high optical absorbance of Hb green and yellow wavelength range, the near-infrared spectroscopy measurements are for 90% confined to microvasculature with a diameter of less than 100 μm, that is, arterioles, capillaries, and venules.

Statistical analysis

Statistical analysis was performed using computer software (GraphPad Prism 5.0, GraphPad Software, La Jolla, CA). Comparative analysis of data sets obtained at different time points was performed using Wilcoxon matched-pairs test. All data are presented as mean ± SD and differences between time points were considered significant at $p < 0.05$ and denoted with an asterisk.

RESULTS

Patient characteristics

The patient characteristics and operative variables of both groups are presented in Table 1. Coexisting diseases are given in Table 2. No statistical significant differences between Group A (SDF imaging) and Group B (spectrophotometry) were identified with respect to the demographic characteristics and operative variables.

Effects of CPB during cardiac surgery

CPB was associated with a change from pulsatile to nonpulsatile flow, an increase in cardiac output from 4.3 ± 0.3 L/min as pumped by the heart to 4.7 ± 0.5 L/min ($p < 0.01$) as generated by the CPB roller-pump and a decrease of mean arterial pressure from 71.2 ± 5.2 mmHg before CPB to 51 ± 4.8 mmHg ($p < 0.01$) 10 minutes after the onset of CPB.

TABLE 1. Patient characteristics and operative variables

Characteristics	Group A (n = 12)	Group B (n = 12)	Significance
Demographics			
Age (years)	64 ± 11	64 ± 12	NS
Sex (male:female)	7:5	10:2	
Body surface area (m^2)	1.81 ± 0.4	1.83 ± 0.5	NS
ASA score	3	3	NS
Surgical procedure			
Isolated CABG	8	7	
Isolated valve replacement	1	2	
CABG and valve replacement	3	3	
Operative variables			
Number of CABG procedures	2.3 ± 0.6	2.6 ± 0.9	NS
CPB time (min)	92 ± 19	96 ± 27	NS
Aortic clamp time (min)	69 ± 22	71 ± 29	NS
RBC units/patient	1.8 ± 0.8	2.3 ± 0.9	NS
RBC unit storage time (days)	18 ± 2	18 ± 3	NS

ASA = American Society of Anesthesiology; CABG = coronary artery bypass graft surgery.

TABLE 2. Coexisting conditions

Diagnosis	Group A (n)	Group B (n)
Hypertension	2	4
Hypercholesterolemia	2	4
Diabetes	3	2
Peripheral vascular disease	3	5

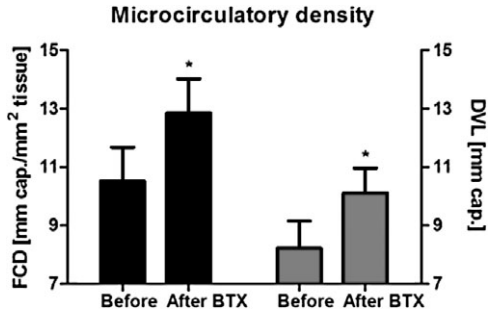

Fig. 1. Microcirculatory density, expressed as FCD (mm capillary [cap.]/mm² tissue) and DVL (mm capillary [cap.]), before and 30 minutes after blood transfusion (BTX). *p < 0.05 for before versus after BTX.

The addition of oxygenator priming solution (1850 mL) to the circulation caused significant hemodilution reflected by decreased systemic Hb content and hematocrit (Hct). Systemic Hb content decreased in Group A from 6.2 ± 1.1 to 4.4 ± 1.0 mmol/L ($p < 0.01$) and in Group B from 6.5 ± 0.9 to 4.9 ± 0.7 mmol/L ($p < 0.01$). Systemic Hct decreased in Group A from 25.1 ± 2.2% to 20.2 ± 2.1% ($p < 0.01$) and in Group B from 26.4 ± 1.3% to 23.3 ± 2.5% ($p < 0.01$). Blood temperature rapidly decreased from 36.6 ± 0.4 to 32.7 ± 0.9°C ($p < 0.01$) at 10 minutes after the onset of CPB.

Effects of RBC transfusion during CPB

At the macrocirculatory level, RBC transfusion caused a significant increase in mean arterial pressure, systemic Hb content, and Hct. Mean arterial pressure increased from 60.1 ± 10.9 to 66.1 ± 7.7 mmHg ($p = 0.03$) in Group A and from 65.2 ± 12.1 to 73.2 ± 10.3 mmHg in Group B. Systemic Hb content increased in Group A from 4.4 ± 1.0 to 5.3 ± 0.8 mmol/L ($p < 0.01$) and in Group B from 4.9 ± 0.7 to 5.6 ± 1.0 mmol/L ($p < 0.01$). Systemic Hct increased in Group A from 20.2 ± 2.1% to 22.7 ± 2.2% ($p < 0.01$) and in Group B from 23.3 ± 2.5% to 25.5 ± 1.9% ($p < 0.01$).

At the microcirculatory level, RBC transfusion resulted in increased FCD (from 10.5 ± 1.2 to 12.9 ± 1.2 mm capillary/mm² tissue, $p < 0.01$, Fig. 1) and DVL (from 8.2 ± 0.9 to 10.1 ± 0.9 mm, $p < 0.01$, Fig. 1) as detected using SDF imaging. MFI was not affected by RBC transfusion in both small- (from 2.97 ± 0.03 to 2.96 ± 0.03 AU, $p = 0.95$, Fig. 2) and medium-sized vessels (from

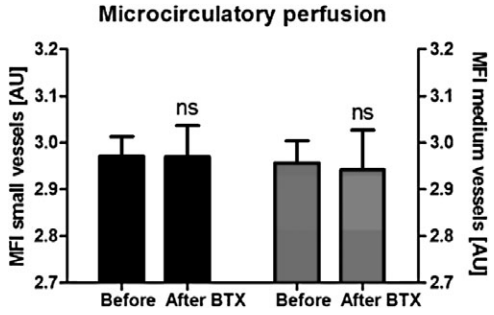

Fig. 2. Microcirculatory perfusion, expressed in MFI (AU), in small- and medium-sized vessels before and 30 minutes after blood transfusion (BTX). ns = not significant.

Fig. 3. Microcirculatory Hb (MC Hb) content [AU] en saturation [%] before and 30 minutes after blood transfusion (BTX). *p < 0.05 for before versus after BTX.

2.97 ± 0.04 to 2.94 ± 0.05 AU, $p = 0.57$, Fig. 2). In concert with the SDF measurements, spectrophotometry showed that microcirculatory Hb content increased from 61.4 ± 5.9 to 70.0 ± 4.7 AU ($p < 0.01$, Fig. 3) and that microcirculatory Hb oxygen saturation increased from 65.6 ± 8.3% to 68.6 ± 8.4% ($p = 0.06$, Fig. 3).

DISCUSSION

In the past decade transfusion medicine has been under intensive evaluation. Although transfusion therapy has been used worldwide for a long time, there are many issues open for debate. Among these issues, the efficacy of RBC transfusions has an essential place. To our knowledge, no clinical study has yet examined whether RBC transfusions improve microcirculatory perfusion and oxygenation in CPB-assisted cardiac surgery patients. A major problem in such investigations until now has been the lack of appropriate noninvasive techniques to be used in vivo. In the past decade, the development of novel, noninvasive technologies, such as SDF imaging and spectrophotometry, allowed clinicians and researchers to perform bedside monitoring of sublingual microcirculatory networks. These developments help physicians to understand the underlying mechanisms of several disease

states and set new therapeutic endpoints and markers to monitor tissue oxygenation more intensively and to detect and correct tissue hypoxia earlier.

The aim in this study was to investigate the effects of leukoreduced allogeneic RBC transfusions on sublingual microcirculatory density, perfusion, Hb content, and oxygen saturation using SDF imaging and reflectance spectrophotometry, in a host with (relatively) healthy microcirculation, that is, in patients undergoing CPB-assisted cardiac surgery. We have shown that RBC transfusions: 1) improve the systemic circulation and oxygen-carrying capacity, 2) improve sublingual microcirculatory density (FCD and DVL) but not the perfusion velocity (MFI), and 3) cause an increase in microcirculatory oxygen saturation.

Large retrospective studies in both North America and Europe investigated transfusion practices and compared outcomes of restrictive and liberal transfusion practices.[18-20] The TRICC study[18] was the first to demonstrate the possible detrimental effects of blood transfusions in such a big population. The authors investigated the outcomes of 838 patients admitted to Canadian intensive care units (ICUs) managed with restrictive (transfusion trigger of 7 g/dL and target Hb of 7-9 g/dL) and liberal (transfusion trigger of 10 g/dL and target Hb of 10-12 g/dL) transfusion practice. They have shown that both 20-day ICU and hospital mortality rates were lower in the restrictive group but the differences were only significant for hospital mortality. In the ABC study,[19] a European cohort study carried out over 2 weeks in 3534 patients admitted to 146 western European ICUs, Vincent and coworkers reported higher ICU and overall mortality rates in patients who had received a blood transfusion than in those who had not. Additionally, in matched patients in a propensity analysis the 28-day mortality rate was 23% among transfused patients and 17% among nontransfused patients. Following in 2004, in the CRIT study[20] in which 4892 patients admitted to ICUs in the United States were observed, the mean pretransfusion Hb concentration was found to be 8.6 g/dL, which is similar to the TRICC and ABC studies. The CRIT study confirmed the results of the TRICC and ABC study by showing that the number of RBC transfusions was an independent predictor of worse clinical outcome and was independently associated with longer ICU and hospital lengths of stay and an increase in mortality.

These results are supported by various other studies. Kuduvalli and colleagues,[4] in 3024 cardiac surgery patients, have reported an association between increased risk of mortality and perioperative transfusions, with a large proportion of deaths occurring within 30 days. In 10,289 patients undergoing coronary artery bypass grafting, a significant reduction in survival was shown in those patients who have received blood transfusions and transfusions were found to be associated with long-term postoperative mortality and morbidity.[5] In another retrospective cohort study RBC transfusion in patients having cardiac surgery was found to be strongly associated with infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs.[2]

In short, although few conflicting results were presented by the majority of these studies suggested that, with the current transfusion practice and triggers being used at the time of these studies, blood transfusions are associated with a worse outcome in these patients. Whether this finding is related to the adverse effects related to the transfusions or loss of functional RBCs is not clear. Nevertheless this finding made it clear that transfusion therapy is not free of adverse effects and the balance between efficiency and adverse effects should be kept in consideration at all times when a transfusion decision is given. The fact that transfusion therapy could be harmful for the patients, actually forces the clinician to ensure and maximize the efficiency of transfusion therapy. The transfusion trigger used in our study is similar to those in restrictive transfusion strategies in the ABC, CRIT, and TRICC studies, which allow comparison of these findings with other studies.

The efficacy of RBCs can be determined by a number of factors. The presence of white blood cells (WBCs), quality of transfused RBCs, microcirculatory status of the patient, underlying diseases, and related medical interventions, such as hemodilution or surgical procedures or medications may play a role in the success of transfusions in improving tissue oxygenation. The presence of WBCs in transfused units may have an important role in the adverse effects observed in patients and could partly explain the controversial results between different studies. The ABC[19] and CRIT[20] studies, which observed harmful effects and an increased risk of complications and mortality after transfusions, were with nonleukoreduced blood. In contrast, the SOAP[21] study, which included 3147 patients from 198 European ICUs, reported that mortality rate after RBC transfusion was higher but these patients were in general older and had more coexisting diseases. After propensity matching, transfused and nontransfused patients showed no difference in mortality rates, which was in contrast to the other studies. The authors hypothesized that this may be due to the fact that the RBC transfusions were leukoreduced.

Similarly, Hebert and Fergusson[22] showed in a larger retrospective analysis of 14,786 patients before and after the implementation of universal leukoreduction in Canada that there was a decrease in mortality rate in cardiac surgery patients and also a reduction in posttransfusion fever, which was a similar finding to most other studies. Bilgin and coworkers[23] reported in a prospective randomized double-blind study of patients undergoing cardiac valve surgery that there was a reduction in infection rates

and hospital mortality. Fung and colleagues[24] showed the beneficial effects of leukoreduced RBCs for cardiac surgery patients with a decrease in postoperative length of stay.

A controlled trial in the Netherlands was carried out by van de Watering and colleagues[25] and compared leukoreduced and buffy coat–depleted RBC transfusions in patients undergoing coronary artery bypass grafting, with or without valve replacement. The authors found a significant decrease in postoperative infections in patients receiving more than 4 units of blood. Remarkably, in this study, mortality was found to be reduced only in patients that received leukoreduced blood and not in those that received buffy coat–depleted blood. That may be explained by the differences between these two reduction methods; buffy coat–depleted blood contains approximately 10^9 WBCs, whereas leukoreduced blood contains approximately 10^6 WBCs. The results of these studies suggest that presence of WBCs has a role in the outcome of patients who receive transfusions. In this study all transfused blood units were leukoreduced.

In this study, we have shown that leukoreduced RBC transfusions improve microcirculatory density and oxygenation. Decreased intercapillary diffusion distance after transfusion (i.e., increased capillary density) enhances the oxygen transport from the microcirculation to the tissues. Leukoreduced RBC transfusions are therefore successful in correcting the anemic conditions caused by blood loss and hemodilution associated with CPB circulation and anesthesiologic procedures in cardiac surgery patients.

Practical considerations

There were a number of practical considerations pertaining to our study. First, we did not perform the SDF and O2C measurements simultaneously in each patient because the SDF measurements could cause light and movement artifacts that would negatively affect reflectance spectrophotometry measurements. Hence, we have chosen to perform these measurements separately in two different groups. Second, in this study the posttransfusion time point was performed 30 minutes after transfusion, which may have disregarded possible alterations in the late phase. However, we have chosen this time point according to findings in a pilot study.

In this pilot study we have performed SDF and O2C measurements repeatedly for 2 hours after transfusion determined that the microcirculatory alterations were optimally measureable 30 minutes after transfusion. Moreover, later measurements are impractical as therapeutic interventions and changes in the patient's condition would affect the observations. Although no interventions other than RBC transfusion were allowed during the observation period, we cannot completely rule out the fact that these changes may have been influenced by other factors during surgery.

In conclusion, we have shown that, in a host with (relatively) healthy microcirculation, that is, in patients undergoing CPB-assisted cardiac surgery, RBC transfusions: 1) improve the systemic circulation and oxygen-carrying capacity, 2) improve sublingual microcirculatory density (FCD and DVL) but not the perfusion velocity (MFI), and 3) cause an increase in microcirculatory oxygen saturation. These observations suggest that leukoreduced RBC transfusions enhance tissue oxygen availability by reducing diffusion distance and increasing the capillary surface area available for oxygen diffusion and also increasing microcirculatory Hb concentration and saturation.

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CONFLICT OF INTEREST

There is no conflict of interest from all authors.

REFERENCES

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, Shah A. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. Crit Care Med 2005;33:1749-56.
2. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116:2544-52.
3. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608-16.
4. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, Fabri BM, Rashid A. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg 2005;27:592-8.
5. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006;81:1650-7.
6. Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, Herruzo-Avilés A, Camacho-Laraña P, Garnacho-Montero J, Amaya-Villar R. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 2001;119:1461-8.

7. Chelemer SB, Prato BS, Cox PM Jr, O'Connor GT, Morton JR. Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. Ann Thorac Surg 2002;73:138-42.
8. Vamvakas EC, Carven JH. RBC transfusion and postoperative length of stay in the hospital or the intensive care unit among patients undergoing coronary artery bypass graft surgery: the effects of confounding factors. Transfusion 2000;40:832-9.
9. Fergusson D, Khanna MP, Tinmouth A, Hebert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. Can J Anaesth 2004;51:417-24.
10. Vamvakas EC. WBC-containing allogeneic blood transfusion and mortality: a meta-analysis of randomized controlled trials. Transfusion 2003;43:963-73.
11. Sakr Y, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, Creteur J, Gullo A, Vincent JL, De Backer D. Microvascular response to red blood cell transfusion in patients with severe sepsis. Crit Care Med 2007;35:1639-44.
12. Creteur J, Neves AP, Vincent JL. Near-infrared spectroscopy technique to evaluate the effects of red blood cell transfusion on tissue oxygenation. Crit Care 2009;13 Suppl 5:S11.
13. Goedhart PT, Khalilzada M, Bezemer R, Merza J, Ince C. Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 2007;15:15101-14.
14. De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, Dobbe I, Ince C. How to evaluate the microcirculation: report of a round table conference. Crit Care 2007;11:R101.
15. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM; Microcirculatory Alterations in Resuscitation and Shock Investigators. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 2007;49:88-98. e1-2.
16. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care 2005;9:R601-6.
17. Fournell A, Schwarte LA, Scheeren TW, Kindgen-Milles D, Feindt P, Loer SA. Clinical evaluation of reflectance spectrophotometry for the measurement of gastric microvascular oxygen saturation in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2002;16:576-81.
18. Hebert PC. Transfusion requirements in critical care (TRICC): a multicentre, randomized, controlled clinical study. Transfusion Requirements in Critical Care Investigators and the Canadian Critical care Trials Group. Br J Anaesth 1998;81 Suppl 1:25-33.
19. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499-507.
20. Corwin HL. Anemia and blood transfusion in the critically ill patient: role of erythropoietin. Crit Care 2004;8 Suppl 2:S42-4.
21. Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology 2008;108:31-9.
22. Hebert PC, Fergusson DA. Evaluation of a universal leukoreduction program in Canada. Vox Sang 2002;83 Suppl 1:207-9.
23. Bilgin YM, van de Watering LM, Eijsman L, Versteegh MI, Brand R, van Oers MH, Brand A. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation 2004;109:2755-60.
24. Fung MK, Rao N, Rice J, Ridenour M, Mook W, Triulzi DJ. Leukoreduction in the setting of open heart surgery: a prospective cohort-controlled study. Transfusion 2004;44:30-5.
25. van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouter H, Boer F, Harvey MS, Huysmans HA, Brand A. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 1998;97:562-8.

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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BACKGROUND: After cardiac surgery, red blood cell (RBC) transfusion may improve systemic hemodynamics and thereby microvascular blood flow and O_2 delivery (DO_2).

STUDY DESIGN AND METHODS: In a nonrandomized prospective observational study on post–cardiac surgery patients, systemic hemodynamics and microvascular blood flow, vascular density (sidestream dark-field imaging), hemoglobin (Hb) content, and saturation (reflectance spectrophotometry) were measured before and 1 hour after start of transfusion of 1 to 2 units of leukoreduced RBCs (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 (Hb < 10 g/dL) or not (n = 13), respectively.

RESULTS: Systemic Hb was lower and increased in the RBC transfusion but not in gelatin and control groups. There were no differences in changes in systemic DO_2, O_2 uptake, and extraction between groups. RBC transfusion, 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 DO_2 in the sublingual microcirculation, independently of systemic hemodynamics and volume status.

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 hypooxygenation.[1-4] On the other hand, studies in cardiac surgery patients have shown an association between perioperative or postoperative RBC transfusions, even when leukoreduced, and a poor outcome.[5-7]

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

ABBREVIATIONS: DO_2 = O_2 delivery; $HbSO_2$ = hemoglobin O_2 saturation; ICU = intensive care unit; MFI = microvascular flow index; O_2ER = O_2 extraction ratio; PAOP = pulmonary artery occlusion pressure; S_vO_2 = mixed venous O_2 saturation; VO_2 = O_2 consumption.

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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 RBCs 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 Hb 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 this study, we hypothesized that transfusion of normally stored RBCs increases microvascular O_2 delivery (DO_2) by increasing the systemic Hb concentration independently of a volume effect, after cardiac surgery. We therefore compared the effects of RBC transfusion and 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 DO_2, by sidestream dark-field imaging for microcirculatory blood flow and functional vascular density and by reflectance spectrophotometry for Hb content and saturation.

PATIENTS AND METHODS

Patients

This study was a nonrandomized and nonblinded study, approved by the Human Subjects Committee of the Free University Medical Center (Amsterdam, the Netherlands). Written informed consent was obtained from all patients before surgery. Patients were studied within 3 hours after cardiac surgery while still sedated and mechanically ventilated. Patients fulfilled the following inclusion criteria: age more than 18 or less than 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 of more than 35°C, preoperatively obtained informed consent, and not severely hemodynamically compromised with dopamine of less than 5 µg/kg/min and systolic blood pressure of more than 80 mmHg. Exclusion criteria were preterminal illness with less than 24 hours of life expectancy, hypersensitivity to gelatins, and bleeding from drains exceeding 100 mL/hr 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);[16] clinically hypovolemic and nonanemic patients; or nonhypovolemic, nonanemic patients were included in the study and treated with either leukoreduced RBCs (1-2 units, i.e., 200-540 mL) with known storage time (n = 12), 500 mL of gelatin (Gelofusine, gelatin 40 g/L [B. Braun Melsungen AG, Melsungen, Germany], in 154/120 mmol/L 0.9% NaCl; 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 approximately 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 of less than 110 mmHg, a central venous pressure of less than 9 mmHg, a mixed venous O_2 saturation of less than 60%, oligoanuria, and need for vasopressor support.

Protocol

Patients were transferred to the ICU directly after surgery and all measurements were conducted within 3 hours after admission. The study was started as soon as inclusion criteria were met and RBCs, gelatin, or nothing was judged needed by treating physicians. Demographics were recorded and baseline measurements and blood samples were taken over 15 to 30 minutes. Ventilatory settings and vasopressor, inotropic, sedative, and/or analgesic drug doses were unaltered and recorded, as well as durations of mechanical ventilation and stay in the ICU. Before (T = 0) and 1 hour after starting (T = 1) transfusion of 1 to 2 units of RBCs in 15 to 30 minutes, 500 mL of gelatin solution in 15 minutes, 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, mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure (PAOP), and arterial and mixed venous blood gases. The heart rate 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, WI) and end-expiration. For the mean of three 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 Corp., Kobe, Japan), partial O_2 pressure, saturation, and O_2 content

(Rapidlab 865, Bayer Diagnostics, Tarrytown, NY). DO_2, O_2 consumption (VO_2), and O_2 extraction ratio (O_2ER) 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 imaging (MicroScan, Micro Vision Medical, Amsterdam, the Netherlands), which is a noninvasive handheld videomicroscope whose light guide is placed on organ surfaces for direct microscopic observation of the microcirculation.[3,17] 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 0 = no flow, 1 = intermittent flow, 2 = slugging flow, and 3 = continuous flow and expressed as microvascular flow index (MFI). Vascular densities (mm/mm^2) of small- (<25 μm, probably mainly capillaries) and medium-sized (>25 μm, probably mainly venules) vessels were also assessed.

Sublingual microvascular Hb O_2 saturation

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 (arbitrary units [AU]) and Hb O_2 saturation ($HbSO_2$) and was previously used in cardiac surgery.[3,18] 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_2 of the available RBCs. A 1-minute tracing of this spectrum was averaged for $HbSO_2$ values. An increase in $HbSO_2$ indicates improved microvascular DO_2.

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 nonparametric tests (Wilcoxon signed rank test) for changes in the whole group and (Kruskal-Wallis ANOVA) for differences between RBCs, 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 group differed from those in the gelatin group and whether the gelatin group differed from control. The chi-square 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 value of less than 0.05 was considered 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 hours.

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 group but not in the other groups. The increase in cardiac output and central venous pressure in the gelatin group 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. Mixed venous O_2 saturation (S_vO_2) increased and O_2ER decreased in the whole group. There were no differences in changes in DO_2, VO_2, and O_2ER between the groups, while baseline DO_2 and VO_2 were lower in the RBC group than the other groups. All patients had arterial O_2 saturations of 99%, whereas baseline tidal volume 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 in either group. However, the density of medium-sized vessels increased in the RBC compared with the gelatin and control groups. The microvascular Hb concentration and $HbSO_2$ also increased in the RBC group. The effects of gelatin solution did not differ from control.

κ statistics

As shown in Fig. 1, the direction of change in microvascular Hb concentration was similar to the change in systemic Hb

TABLE 1. Patient characteristics*

Characteristic	Group			p value
	RBC (n = 12)	Gelatin (n = 14)	Control (n = 13)	
Age (years)	67 ± 9	67 ± 10	65 ± 12	0.86
Male/female	7/5	10/4	13/0	0.04
BMI (kg/m^2)	29 ± 4	27 ± 5	28 ± 5	0.57
EuroSCORE (additive)	5 ± 2	5 ± 2	5 ± 3	0.73
Length of ICU stay (hr)	29 ± 27	26 ± 9	19 ± 6	0.09
Mechanical ventilation (hr)	12 ± 7	13 ± 12	9 ± 5	0.49
Comorbidity				
Diabetes mellitus	4	3	1	0.56
Hypertension	2	5	6	0.15
COPD	1	0	1	0.55
Current smoking	1	2	4	0.31
Surgery				
CABG	6	8	6	0.26
CABG plus valve surgery	3	0	4	
Valve surgery	3	6	3	
CPB time (min)	142 ± 57	102 ± 32	137 ± 54	0.21
Aortic clamp time (min)	93 ± 50	70 ± 32	103 ± 52	0.51
Treatment				
Infusion volume (mL)	270 ± 203	500		NA
RBC storage time (days)	18 ± 6			NA
Dopamine (µg/kg/min)	1.6 ± 1.6	1.9 ± 1.4[a]	0.6 ± 0.8	0.07

* Data are reported as mean ± SD or number, where appropriate. [a]p = 0.02 vs. control.
BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; NA = not applicable.

TABLE 2. Systemic cardiorespiratory variables*

Variable	Group						p value (Kruskal-Wallis)
	RBC (n = 12)		Gelatin (n = 14)		Control (n = 13)		
	T = 0	T = 1	T = 0	T = 1	T = 0	T = 1	T = 0, T = 1, change
Temperature (°C)	36.2 ± 0.4	36.2 ± 0.5	35.7 ± 1.9	36.1 ± 0.3	36.0 ± 0.5	36.1 ± 0.5	0.69, 0.99, 0.49
Heart rate (bpm)[1]	76 ± 16	74 ± 25	84 ± 9	77 ± 10	75 ± 8	71 ± 9	0.08, 0.40, 0.32
MAP (mmHg)[2]	68 ± 5	79 ± 10	66 ± 10	73 ± 9	75 ± 12	71 ± 21	0.35, 0.08, 0.20
Cardiac output (L/min)	4.3 ± 1.3	3.9 ± 0.9[a]	5.8 ± 2.2	6.2 ± 2.3[b]	5.1 ± 3.1	5.6 ± 2.5	0.001, 0.009, 0.01
CVP (mmHg)[3]	5 ± 2	7 ± 4	5 ± 2	6 ± 2[c]	7 ± 3	6 ± 2	0.48, 0.14, 0.02
PAOP (mmHg)	13 ± 5	13 ± 7	10 ± 4	10 ± 4	11 ± 3	10 ± 3	0.35, 0.59, 0.96
O_2 transport							
P_aO_2 (mmHg)[4]	106 ± 43	117 ± 27	130 ± 42	129 ± 31	99 ± 21	118 ± 28	0.12, 0.47, 0.13
P_vO_2 (mmHg)	36 ± 4	35 ± 5	37 ± 5	39 ± 7	42 ± 9	39 ± 8	0.42, 0.52, 0.48
Hb (g/dL)	8.8 ± 0.5	9.8 ± 0.6[d]	10.7 ± 1.1	10.2 ± 1.3	10.4 ± 0.8	10.2 ± 1.0	<0.001, 0.49, <0.001
S_vO_2 (%)[5]	60 ± 4	64 ± 4	61 ± 4	63 ± 5	60 ± 3	61 ± 3	0.31, 0.38, 0.91
DO_2 (mL/min)	520 ± 145	530 ± 105	684 ± 120	774 ± 228	808 ± 287	776 ± 328	0.001, 0.001, 0.24
VO_2 (mL/min)	202 ± 57	189 ± 41	265 ± 59	281 ± 129	315 ± 99	294 ± 125	0.002, 0.004, 0.63
O_2ER (%)[6]	39 ± 4	36 ± 4	39 ± 4	36 ± 5	39 ± 3	38 ± 3	0.37, 0.91, 0.31
Respiratory variables							
F_iO_2 (%)	46 ± 8	44 ± 9	44 ± 7	42 ± 5	49 ± 12	46 ± 7	0.09, 0.39, 0.85
V_t (mL)	476 ± 57	436 ± 67	477 ± 57	470 ± 67	522 ± 86	511 ± 79	0.03, 0.34, 0.15
PEEP (cmH_2O)	6 ± 2	7 ± 2	6 ± 1	6 ± 2	7 ± 3	7 ± 2	0.45, 0.53, 0.74

* Data are reported as mean ± SD; T = 0 at baseline and T = 1, 1 hour after start of transfusion, infusion, or first measurements. [1]p = 0.02, [2]p = 0.008, [3]p = 0.04, [4]p = 0.04, [5]p = 0.006, and [6]p = 0.005 for change in whole group; [a]p = 0.006 and [d]p < 0.001 for change vs. gelatin; [b]p = 0.01 and [c]p = 0.02 for change vs. control.
CVP = central venous pressure; F_iO_2 = inspiratory O_2 fraction; MAP = mean arterial pressure; P_aO_2 = arterial partial O_2 pressure; PEEP = positive end-expiratory pressure; P_vO_2 = mixed venous PO_2; V_t = tidal volume.

concentration, so that RBC transfusion, in contrast to gelatin or no infusion, increased both. This was also associated with an increase 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 RBCs did not relate to any of these microvascular variables.

DISCUSSION

The main findings of this study are that, after cardiac surgery, RBC transfusion improves systemic and microvascular Hb and $HbSO_2$ at unchanged MFI, thus increasing microvascular DO_2, independently of systemic

TABLE 3. Microvascular hemodynamics*

	Group						
	RBC (n = 12)		Gelatin (n = 14)		Control (n = 13)		p value (Kruskal-Wallis)
Variable	T = 0	T = 1	T = 0	T = 1	T = 0	T = 1	T = 0, T = 1, change
Flow index							
Small	2.2 ± 0.8	2.5 ± 0.4	2.3 ± 0.7	2.4 ± 0.6	2.4 ± 0.8	2.6 ± 0.6	0.52, 0.42, 0.80
Medium	2.7 ± 0.3	2.8 ± 0.2	2.8 ± 0.3	2.7 ± 0.4	2.8 ± 0.3	2.9 ± 0.2	0.52, 0.78, 0.77
Vascular density (mm/mm^2)							
Small	12.5 ± 2.0	12.8 ± 2.7	13.0 ± 3.4	14.2 ± 4.9	12.9 ± 2.8	12.8 ± 1.7	0.97, 0.98, 0.45
Medium	0.5 ± 0.5	0.7 ± 0.4[a]	0.8 ± 0.6	0.6 ± 0.4	0.8 ± 0.5	0.8 ± 0.6	0.29, 0.44, 0.046
Hb (AU)	72 ± 11	78 ± 10[b,c]	77 ± 9	73 ± 10	76 ± 8	71 ± 7	0.44, 0.87, 0.001
$HbSO_2$ (%)	74 ± 12	76 ± 12[d,e]	77 ± 7	75 ± 7	77 ± 6	75 ± 6	0.91, 0.69, <0.001

* Data are reported as mean ± SD; T = 0 at baseline and T = 1, 1 hour after start of transfusion, infusion or first measurements. [a]p = 0.01, [b]p < 0.001, and [d]p = 0.01 for change vs. gelatin and [c]p = 0.008 and [e]p = 0.016 for change vs. control.
AU = arbitrary units.

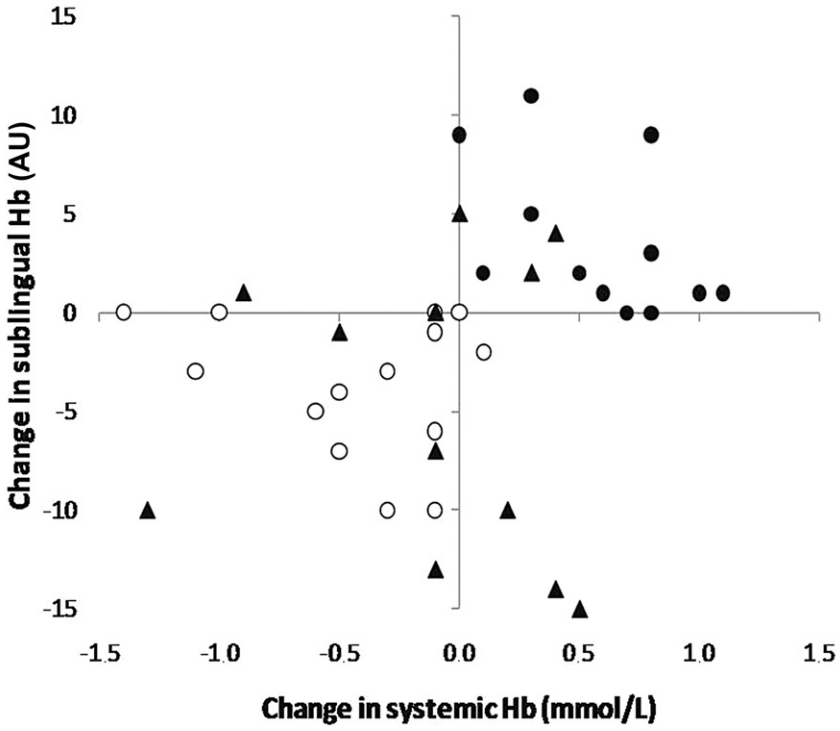

Fig. 1. The change of relative microvascular Hb concentrations of the sublingual microcirculation as function of the change of systemic Hb concentration in cardiac surgery patients after postoperative transfusion of RBC (●) or infusion of gelatin (○) and in control patients (▲). It is shown that changes in microcirculatory Hb were directionally similar to those in systemic Hb (κ = 0.29, p = 0.01), so that RBC transfusion (vs. gelatin and no infusion) increased both. AU = arbitrary units.

hemodynamics and oxygenation. This is associated with recruitment of medium-sized vessels.

Although the increases in S_vO_2 and decreases in O_2ER indicate a higher O_2 supply–demand ratio, changes did not differ between the groups. Infusion of gelatin solution increased cardiac output but not DO_2, because of concomitant hemodilution, as described elsewhere.[19] Indeed, infusion was associated with an unchanged MFI and DO_2 in the microcirculation. This disagrees with the literature on hemorrhagic shock in pigs[20] 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 findings of studies in animals[10,11] and in humans during cardiac surgery[4] that RBC transfusion increases sublingual microvascular density and $HbSO_2$ but not the MFI. The increase in microvascular Hb and (venular) $HbSO_2$ at unchanged MFI otherwise implies an increase in microvascular DO_2 rather than arteriovenous shunting, even though microvascular was higher than S_vO_2. Systemic DO_2 did not increase with RBC transfusion because the increase in Hb was offset by a decrease in cardiac output, at unchanged tissue requirements (VO_2), as commonly observed and attributable to a rise in blood viscosity and systemic vascular resistance.[1,14] However, RBC transfusion may increase systemic DO_2 (at unchanged O_2 uptake) and capillary perfusion when low at the start in critically ill, septic patients.[8] In the study by Créteur and colleagues,[9] near-infrared spectroscopy–derived tissue O_2 variables did not increase by RBC transfusion in septic and nonseptic 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 DO_2 by Hb than by systemic hemodynamics and volume status. This agrees with experimental conditions, at least when Hb O_2 affinity is normal.[10,12,16,21] Apparently, the medium-sized vessels in

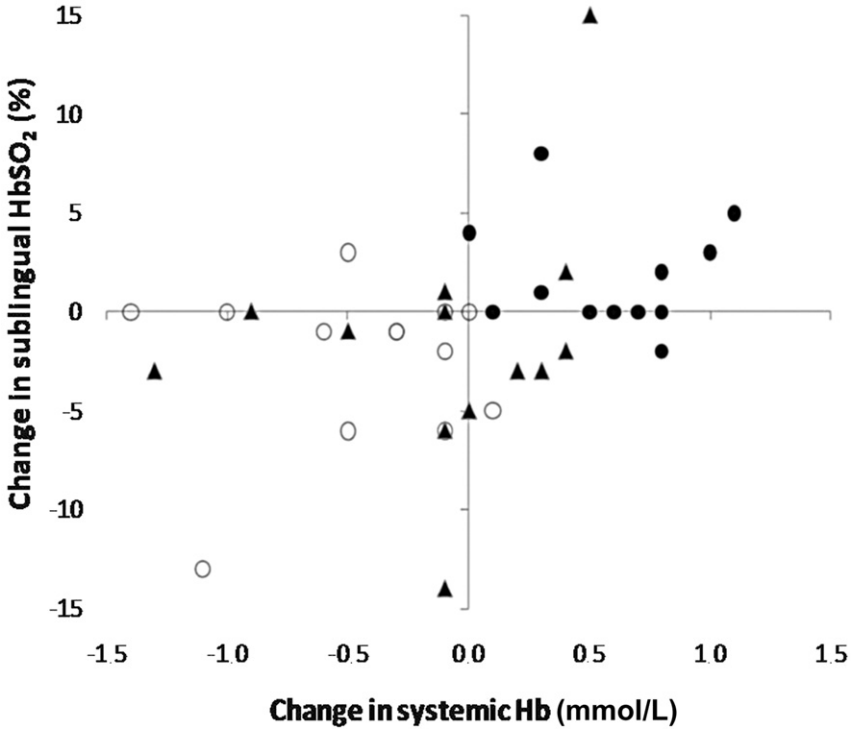

Fig. 2. The relation between the changes in microvascular sublingual $HbSO_2$ and those in systemic Hb concentrations in cardiac surgery patients after postoperative transfusion of RBCs (●) or infusion of gelatin (○) and in control patients (▲). It is shown that changes in microcirculatory $HbSO_2$ were directionally similar to those in systemic Hb ($\kappa = 0.22$, $p = 0.04$), so that RBC transfusion (vs. gelatin and no infusion) increased both.

the microcirculation, most likely venules, accommodated for the increased numbers of RBCs 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 nonleukoreduced, RBC transfusions after cardiac surgery may be attributable to adverse effects that do not relate to the microcirculation, unless storage times are unduly prolonged.[1-4,10,11] Indeed, storage-induced stiffening of RBC may compromise rather than increase microvascular variables.[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 variables, as noted before.[8,9]

Previously, we investigated the sublingual microcirculation during normovolemic hemodilution, after start of extracorporeal pump perfusion in coronary artery surgery patients, and found an increased microvascular MFI and $HbSO_2$ and a reduction of capillary density.[3] The fact 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 an increase (rather than a decrease) in cardiac output in the latter. Also, microvascular DO_2 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 average, fluid responsive, that is, 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 hours for changes during pump perfusion to gradually normalize in the ICU.[2-4] We did not observe an effect of pump versus off-pump perfusion, described previously.[2]

Apart from relatively small groups, limitations of the current study include a nonrandomized design, since randomization for RBC transfusion would be barely feasible, even though indications for transfusion after cardiac surgery are relatively poorly established.[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_2 variables before 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 an increase in systemic Hb increases medium-sized vascular density and DO_2 in the sublingual microcirculation, independently of systemic hemodynamics and volume status. The clinical implications need further study.

CONFLICT OF INTEREST

None of the authors have a conflict of interest or financial involvement with this manuscript.

REFERENCES

1. Vincent JL, Sakr Y, De Backer D, Van der Linden P. Efficacy of allogeneic red blood cell transfusions. Best Pract Res Clin Anaesthesiol 2007;21:209-19.
2. De Backer D, Dubois M-J, Schmartz D, Koch M, Ducart A,

Barvais L, Vincent J-L. Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. Ann Thorac Surg 2009;88:1396-403.
3. Atasever B, Boer C, Goedhart P, Biervliet J, Seyffert J, Speekenbrink R, Schwarte L, de Mol B, Ince C. Distinct alterations in sublingual microcirculatory blood flow and hemoglobin oxygenation in on-pump and off-pump coronary artery bypass graft surgery. J Cardiothor Vasc Anesth 2011;25:784-90.
4. Yuruk K, Almac E, Bezemer R, Goedhart P, De Mol B, Ince C. Blood transfusions recruit the microcirculation during cardiac surgery. Transfusion 2011;51:961-7.
5. Reeves BC, Murphy GJ. Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery. Curr Opin Cardiol 2008;23:607-12.
6. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, Marrin CA, Helm RE Jr, Leavitt BJ, Morton JR, Charlesworth DC, Clough RA, Hernandez F, Frumiento C, Benak A, DioData C, O'Connor GT; Northern New England Cardiovascular Disease Study Group. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 2009;108:1741-6.
7. Möhnle P, Snyder-Ramos SA, Miao Y, Kulier A, Bttiger BW, Levin J, Mangano DT; Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. Intensive Care Med 2011;37:97-109.
8. Sakr Y, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, Créteur J, Gullo A, Vincent JL, De Backer D. Microvascular response to red blood cell transfusion in patients with severe sepsis. Crit Care Med 2007;35:1639-44.
9. Créteur J, Neves AP, Vincent JL. Near-infrared spectroscopy technique to evaluate the effects of red blood cell transfusion on tissue oxygenation. Crit Care 2009;13 Suppl 5:S11.
10. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 2004;44:1626-34.
11. Arslan E, Sierko E, Waters JH, Siemionow M. Microcirculatory hemodynamics after acute blood loss followed by fresh and banked blood transfusion. Am J Surg 2005;190:456-62.
12. Cabrales P. Effects of erythrocyte flexibility on microvascular perfusion and oxygenation during acute anemia. Am J Physiol Heart Circ Physiol 2007;293:H1206-H1215.
13. Raat NJ, Ince C. Oxygenating the microcirculation: the perspective from blood transfusion and blood storage. Vox Sang 2007;93:12-8.
14. Slight RD, Alston P, McClelland DB, Mankad PS. What factors should we consider in deciding when to transfuse patients undergoing elective cardiac surgery? Trans Med Rep 2009;23:42-54.
15. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2011;(3):CD001319.
16. Cabrales P, Tsai AG, Intaglietta M. Modulation of perfusion and oxygenation by red blood cell oxygen affinity during acute anemia. Am J Respir Crit Care Med 2008;38:354-61.
17. Goedhart PT, Khalilzada M, Bezemer R, Merza J, Ince C. Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 2007;15:15101-14.
18. Fournell A, Schwarte LA, Scheeren TW, Kindgen-Milles D, Feindt P, Loer SA. Clinical evaluation of reflectance spectrophotometry for the measurement of gastric microvascular oxygen saturation in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2002;16:576-81.
19. Trof RJ, Sukul SP, Twisk JW, Girbes AR, Groeneveld AB. Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolaemia. Intensive Care Med 2010;36:697-701.
20. Maier S, Holz-Hölzl C, Pajk W, Ulmer H, Hengl C, Dünser M, Haas T, Velik-Salchner C, Fries D, Greiner A, Hasibeder W, Knotzer H. Microcirculatory parameters after isotonic and hypertonic colloidal fluid resuscitation in acute hemorrhagic shock. J Trauma 2009;66:337-45.
21. Cabrales P, Intaglietta M, Tsai AG. Transfusion restores blood viscosity and reinstates microvascular conditions from hemorrhagic shock independent of oxygen carrying capacity. Resuscitation 2007;75:124-34.

Red blood cell transfusions and tissue oxygenation in anemic hematology outpatients

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BACKGROUND: There is little clinical evidence that red blood cell (RBC) transfusions improve oxygen availability at the microcirculatory level. We tested the hypotheses that anemia in chronically anemic patients with relatively healthy microcirculation would be associated with low tissue hemoglobin (Hb) and tissue oxygenation levels and that these conditions would be improved after RBC transfusions.

STUDY DESIGN AND METHODS: Near-infrared spectroscopy (NIRS) was used to determine tissue oxygen saturation (StO_2) and tissue Hb index (THI; an index of the amount of Hb in the NIRS measurement volume) in the thenar eminence and sublingual tissue before and 30 minutes after RBC transfusions in 20 chronically anemic hematology outpatients. Data are presented as median (25%-75%).

RESULTS: The patients received three (two to three) bags of RBCs in saline-adenine-glucose-mannitol with an age of 21 (7-21) days, which was infused intravenously at the rate of 0.7 bag/hr. RBC transfusions significantly increased hematocrit level from 26% (24%-28%) to 32% (30%-34%; $p < 0.0001$), Hb level from 8.2 (7.6-8.9) g/dL to 11.0 (9.9-11.8) g/dL ($p < 0.0001$), whole blood viscosity from 3.4 (3.1-3.5) mPa/sec to 4.2 (4.0-4.5) mPa/sec ($p < 0.0001$), thenar StO_2 from 81% (80%-84%) to 86% (81%-89%; $p = 0.002$), thenar THI from 11.2 (9.3-13.3) AU to 13.7 (9.7-15.3) AU ($p = 0.024$), sublingual StO_2 from 86% (81%-89%) to 91% (86%-92%; $p < 0.0001$), and sublingual THI from 15.2 (13.0-17.4) AU to 17.2 (13.5-19.7) AU ($p = 0.040$).

CONCLUSION: Although anemia in chronically anemic hematology outpatients was not associated with low StO_2 and THI levels, RBC transfusions were successful in improving these variables.

The primary goal of red blood cell (RBC) transfusions is to increase hematocrit (Hct) and blood hemoglobin (Hb) levels, thereby improving microcirculatory Hb availability and, ultimately, tissue oxygenation. To date, only a few clinical studies have investigated the effects of RBC transfusions on peripheral microcirculation. In a study by Sakr and colleagues[1] in septic patients, no changes were found after RBC transfusions in microcirculatory density and perfusion when measured sublingually using orthogonal polarization spectral imaging. Similarly, Creteur and colleagues[2] found no effect of RBC transfusions on microcirculatory oxygenation in septic and nonseptic intensive care patients, as measured in the thenar eminence using near-infrared spectroscopy (NIRS). Contrary to these studies, we recently demonstrated improved microcirculation upon RBC transfusion in cardiac surgery patients.[3] The contrasting results of these studies may be related either to the impaired microcirculation in septic patients compared with cardiac surgery patients or to the fact that intensive care patients are chronically (or progressively) anemic, while cardiac surgery patients suffer from a more acute onset of anemia.[4] In this respect, it has been shown

ABBREVIATIONS: MAP = mean arterial pressure; NIRS = near-infrared spectroscopy; StO_2 = tissue oxygen saturation; THI = tissue hemoglobin index.

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that chronic anemia leads to the development of compensatory mechanisms, such as an increased release of oxygen, due to higher levels of 2,3-diphosphoglycerate acid.[5]

In this study, we focused on the latter factor and investigated the effects of RBC transfusions on microcirculatory oxygenation and Hb availability in anemic hematology outpatients, a chronically anemic patient group with relatively healthy microcirculation (compared with that of sepsis patients). We tested the hypotheses that anemia in these patients would be associated with low levels of tissue oxygen saturation (StO_2) and a low tissue Hb index (THI) and that these conditions would improve after RBC transfusions. The THI reflects the amount of Hb in the NIRS measurement volume. This variable depends on both the systemic Hb level, which is low because these patients are anemic, and the peripheral vascular tone (i.e., vasoconstriction decreases THI and vasodilation increases THI). In this light, we expected that, as with the systemic Hb level, THI would be low in anemic patients. Because StO_2 reflects mainly microcirculatory oxygenation, this variable indicates the balance between microcirculatory oxygen delivery and tissue oxygen consumption. Hypothesizing that these patients would have a low THI, we also expected that the StO_2 would be low. In this study, we aimed to identify whether the chronic nature of anemia is the limiting factor in the efficacy of RBC transfusions in some anemic patient groups.

MATERIALS AND METHODS

This study protocol was approved by the institutional medical ethics committee of the Academic Medical Center of the University of Amsterdam. Written informed consent was obtained from all participating patients. This study was performed in compliance with the principles established in the Helsinki Declaration.

Patients

Anemic hematology outpatients requiring RBC transfusions were considered eligible for participation in this study and were recruited during a 2-month period. The threshold for transfusion was set at a Hb level of less than 9.6 g/dL according to standard clinical practice in the Department of Clinical Hematology of the Academic Medical Center and Dutch transfusion guidelines (CBO guidelines 2011, p. 117).[6] Transfusion was stopped after reaching this threshold or after infusion of 3 RBC units. RBC units were prepared according to the standards of Sanquin, the Netherlands national blood bank. The units contained concentrated RBCs obtained after centrifuging whole blood to remove the buffy coat, adding saline-adenine-glucose-mannitol solution, and filtering out the white blood cells (WBCs).[6,7] Upon arrival at the short-stay center for RBC transfusions and after a cross-match blood examination, all participants were subjected to the same investigational procedures, that is, standard determination of venous blood (gas) and hemodynamic variables and NIRS measurements that were performed sublingually and in the thenar eminence, as described below.

NIRS

The patients were placed in a semisupine (30° head-up) position in a hospital bed with their hands (palm up) and arms passively maintained at heart level. The arm opposite to the infusion arm was used in the NIRS measurements. A NIRS device (InSpectra 650, Hutchinson Technology, Hutchinson, MN) equipped with a 15-mm probe was used to measure StO_2 (%) and THI (arbitrary units [AU]) noninvasively before and 30 minutes after blood transfusion in the thenar eminence, as previously described.[3,8] For the sublingual NIRS measurements, an identical probe was used, which was placed on the sublingual mucosa parallel to the frenulum linguae on the same side as the thenar measurements. The spectrometer uses a reflectance mode probe with a 1.5-mm optical fiber to illuminate tissue and a 0.4-mm optical fiber, which is spaced 15 mm from the illuminating fiber, to detect backscattered light. The NIRS measurement depth is estimated as approximately half of the distance between the illumination and detection fibers.[9-11] Both the StO_2 and the THI calculations from the NIRS signal have been validated by Myers and colleagues.[9,12]

Whole blood viscosity assessment

Whole blood was collected in sterile blood tubes, each of which contained 10 mL of blood and 18 mg of K2EDTA, as an anticoagulant. A Couette low-shear viscometer (Contraves LS-30, proRheo GmbH, Althengstett, Germany) was used to measure whole blood viscosity at shear rates of 0.87, 2.19, 5.49, 10.15, 47.1, and 87/sec, in decreasing order.[13] All measurements were performed at a stable temperature of 37°C and were completed within 1 hour of the time that the blood sample was collected.

Statistical analysis

Statistical analysis was performed using computer software (Prism 5.0, GraphPad Software, La Jolla, CA). The Wilcoxon matched-pairs test was used for comparative analysis of data sets obtained before and after RBC transfusion. All data are presented as median values followed by the 25% to 75% range in parentheses. Differences were considered significant at p values of less than 0.05.

RESULTS

Twenty consecutive anemic clinic outpatients (11 males and 9 females) with various hematologic malignancies

with an age of 65 (60-68; Table 1) years requiring RBC transfusions participated in this study. The patients received three (two to three) bags of RBCs with an age of 21 (7-21) days, which were infused intravenously at the rate of 0.7 bags/hr.

All NIRS measurements were performed successfully and without any inconvenience or discomfort to the patients. Hct, Hb, whole blood viscosity, and hemodynamic variables before and 30 minutes after RBC transfusions are presented in Table 2. RBC transfusions increased the Hct from 26% (24%-28%) to 32% (30%-35%; $p < 0.0001$), Hb from 8.2 (7.6-8.9) g/dL to 11.0 (9.8-11.8) g/dL ($p < 0.0001$; Fig. 1A), and whole blood viscosity from 3.4 (3.1-3.5) mPa/sec to 4.2 (4.0-4.5) mPa/sec ($p < 0.0001$). Mean arterial pressure (MAP) increased from 84 (77-92) mmHg to 94 (84-107) mmHg ($p = 0.006$), and heart rate decreased slightly from 82 (71-91) bpm to 78 (71-87) bpm ($p = 0.088$; Fig. 1B).

After the RBC transfusion, the thenar (Fig. 1C) and sublingual (Fig. 1D) StO_2 and THI increased significantly. The thenar StO_2 and THI increased from 81% (80%-84%) to 86% (81%-89%; $p = 0.002$) and from 11.2 (9.3-13.3) AU to 13.7 (9.7-15.3) AU ($p = 0.024$), respectively. The sublingual StO_2 and THI increased from 86% (81%-89%) to 91% (86%-92%; $p < 0.0001$) and from 15.2 (13.0-17.4) AU to 17.2 (13.5-19.7) AU ($p = 0.040$), respectively.

TABLE 1. Patient characteristics*

Demographics	
Age (years)	65 (60-68)
Sex (male : female)	11:9
Underlying disease (number of patients)	
Myelodysplastic syndrome	7
Myelofibrosis	4
Multiple myeloma	3
Acute myeloid leukemia	2
Chronic myeloid leukemia	1
Chronic lymphocytic leukemia	1
Metastasis bleeding	1
Non-Hodgkin's lymphoma	1
Transfusion characteristics	
Number of RBC bags	3 (2-3)
Age of transfused blood (days)	21 (7-21)

* Data are presented as median (25%-75%) unless indicated otherwise.

DISCUSSION

In this study, we investigated the effects of RBC transfusions on microcirculatory oxygenation in chronically anemic patients with relatively healthy microcirculation. We hypothesized that anemia in these patients would be associated with low StO_2 and Hb availability (THI), which would increase after the RBC transfusion. This is an important issue because studies addressing the efficacy of RBC transfusion at the microcirculatory level have only concerned critically ill patients and showed little or no effect of RBC transfusions on microcirculation.[1,2] In this study, we demonstrate that, although anemia in chronically anemic outpatients was not associated with low StO_2 and THI levels, RBC transfusions were successful in improving these conditions.

Although RBC transfusions successfully improved such conditions as Hct and Hb levels, whole blood viscosity, and MAP,[2,3,14,15] the efficacy of RBC transfusions in improving microcirculation and, ultimately, tissue oxygenation is poorly understood. Recently, microcirculation has gained increasing attention as an independently functioning physiological compartment in which the roles of the glycocalyx, RBCs, and WBCs are shifted from passive components to active mediators.[2,3]

Blood transfusion practice and policies have been a topic of debate since several large clinical studies demonstrated the potentially harmful effects of allogeneic blood transfusions, such as infection transmission, immunosuppression, inflammation and coagulation in the lung, and atrial fibrillation.[16-19] These studies concluded that restrictive transfusion thresholds and regimens contribute to better clinical outcomes. Whether the adverse effects of blood transfusions are due to the composition of the transfused blood (e.g., leukoreduced vs. leukodepleted blood) or other factors (e.g., age of the transfused blood) remains elusive. Nevertheless, the decision of whether to give a blood transfusion remains a consideration of the beneficial effects of transfusion, for example, increasing the systemic oxygen-carrying capacity, microcirculation, and ultimately, tissue oxygenation versus the adverse effects of transfusion. In this line of reasoning, blood transfusion not only improves systemic Hct but also increases whole blood viscosity, as we have shown here.

TABLE 2. Blood and hemodynamic variables

		Before transfusion			After transfusion				
Variable	Unit	Median	25th	75th	Median	25th	75th	p value	Normal range
Hct	%	26	24	28	32	30	35	<0.0001	36-51
Hb	g/dL	8.2	7.6	8.9	11.0	9.8	11.8	<0.0001	12.1-17.7
Blood viscosity	mPa/sec	3.4	3.1	3.5	4.2	4.0	4.5	<0.0001	3.0-4.0
Systolic blood pressure	mmHg	135	116	147	145	120	158	0.067	90-140
Diastolic blood pressure	mmHg	72	61	80	77	73	85	0.009	60-80
MAP	mmHg	84	77	91	94	84	107	0.006	70-90
Heart rate	bpm	82	71	91	78	71	87	0.088	60-90
Temperature	°C	36.9	37.7	37.1	37.1	36.9	37.6	0.008	35.5-37.5

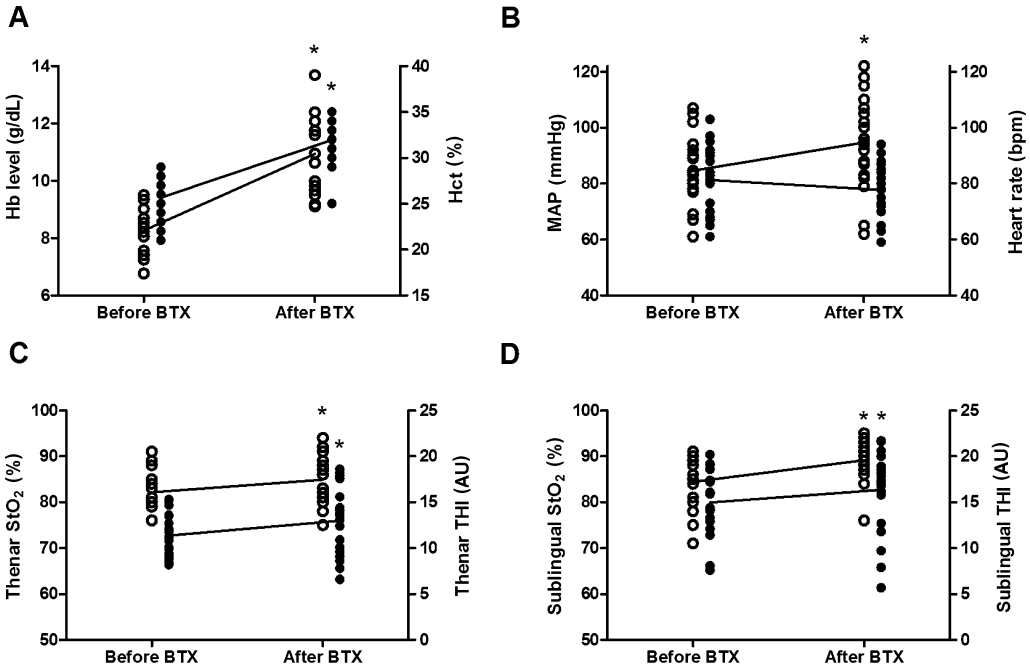

Fig. 1. (A) Hb (g/dL; ○) and Hct (%; ●) levels before and after transfusion; (B) MAP (mmHg; ○) and heart rate (bpm; ●) before and after transfusion; (C) thenar StO_2 (%; ○) and THI (AU; ●) before and after transfusion; and (D) sublingual StO_2 (%; ○) and THI (AU; ●) before and after transfusion. BTX = blood transfusion; *$p < 0.05$ versus before BTX.

This increase in viscosity, in turn, stimulates microvascular perfusion as a result of shear stress-induced vasodilation, as described by Lenz and colleagues.[20]

To date, only a few studies have investigated the direct effects of RBC transfusions on peripheral microcirculation,[1-3,21] and only two studies have shown a beneficial effect of RBC transfusions on microcirculation in adults[3] and anemic preterm infants.[21] The contrasting results of these studies might be explained by the studied patient populations because the studies showing no effect of RBC transfusions were carried out in (septic) intensive care patients in whom the microcirculation is significantly impaired with endothelial dysfunction and abnormal endogenous RBCs.[1,2,4,22] This microcirculatory dysfunction is much less prevalent in surgical patients[3] and preterm infants,[21] possibly explaining the discrepancy between the different studies.

In addition to differences in the microcirculation caused by systemic inflammatory responses, the chronic nature of anemia also may limit the efficacy of RBC transfusions on microcirculatory oxygenation. Therefore, we studied the effects of RBC transfusions on microcirculatory oxygenation in anemic outpatients with a hematologic malignancy but with relatively healthy microcirculation (compared with that of sepsis patients). We showed that the microcirculatory oxygenation and Hb availability were slightly but significantly increased after RBC transfusions. Although the THI and StO_2 increases were modest, this was a highly consistent finding. The sensitivity of both variables to anemia and blood transfusion has been questioned.[2] Here we show that blood transfusion did significantly improve StO_2 and THI, but whether the small changes in THI or StO_2 are of any clinical significance remains to be established. In intensive care patients, blood transfusion did not improve these NIRS variables. Thus, in this study, we have found that there is a difference in response to blood transfusion between intensive care patients and hematology outpatients. However, the mechanisms preventing blood transfusions from effectively reaching the microcirculation in intensive care patients are yet unknown.

This study reports on the use of NIRS on multiple locations to examine the effect of RBC transfusions and introduces the sublingual site for NIRS measurements. Although multisite NIRS measurements have been described before,[8,23,24] analysis of sublingual tissue to examine the effects of RBC transfusions on microcirculation was not performed previously. A study by Yuruk and coworkers[3] applied a spectroscopic technique similar to the NIRS technique used here; however, due to the different wavelength range and probe spacing used in their study, a much smaller measurement volume was captured. Furthermore, to our knowledge, THI has not been used to describe the effects of RBC transfusions at the microcirculatory level. Because THI reflects microcirculatory oxygen-carrying capacity in tissue, this variable is important in studying the effects of RBC transfusions. Previously, NIRS has been employed to identify hypoperfu-

sion and to guide resuscitation in trauma patients.[25,26] Cohn and coworkers[25] reported no differences in StO_2 measurements in the thenar between trauma patients and healthy volunteers. Crookes and coworkers[26] showed that thenar StO_2 values could reflect severe hypovolemic shock, but could not identify mild or moderate shock. Furthermore, studies in healthy volunteers have also shown that StO_2 and THI respond poorly to changes in volume status.[23,27] In one study, 500 mL of blood each was donated by healthy volunteers, and no significant changes in StO_2 were observed.[27] In another study on healthy volunteers subjected to lower-body negative pressure (a model in which application of a vacuum to the lower body shifts blood from the upper to the lower body, creating central hypovolemia), StO_2 and THI levels were shown to decrease only slightly.[23] Altogether, it seems that moderate changes in patient volume changes are poorly reflected by peripherally measured StO_2 and THI levels.

Although the development of NIRS has recently opened the field of bedside monitoring of tissue oxygenation (StO_2) and Hb content (THI) at the microcirculatory level in a variety of patient populations, the interpretation of the measurements should be done with great care. NIRS has been used for the detection of sepsis and as a predictor of patient outcomes.[28-30] NIRS has, moreover, been employed in trauma patients to identify tissue hypoperfusion and to guide resuscitation.[25,26] However, the relative contribution of the arterioles, capillaries, and venules to the NIRS measurement is unknown, which impedes the full physiological interpretation of the StO_2 and THI values in separate microvascular compartments. Furthermore, the NIRS technology is not able to measure flow, which further limits the interpretation of the measurements because flow is a major determinant of tissue oxygenation. Another important consideration is the interpretation of THI, which does not reflect only systemic Hct and Hb levels but also depends on the peripheral (micro)vascular tone.[31] Nonetheless, although baseline StO_2 and THI levels in our anemic outpatients were within the normal range,[8,23] the values associated with both variables increased after RBC transfusions, indicating that transfusions can effectively improve microcirculatory oxygenation in outpatients with hematologic malignancies.

A possible limitation of our study may be that we selected anemic outpatients with various hematologic malignancies, meaning that we cannot exclude the influence of different forms of therapy before this study, such as erythropoietin and high-dose chemotherapy, which may have affected the microcirculation. However, since the baseline microcirculatory oxygenation appeared to be within the normal range and none of the patients was treated with chemotherapy at the time of the study, we consider this effect to be minor. Furthermore, for this study, a relatively high Hb threshold was applied compared with other anemic patient groups. However, according to Dutch guidelines and the transfusion policy of the Department of Clinical Hematology, this relatively old patient group receives RBC transfusions at an Hb level of less than 9.6 g/dL.[6] Although the threshold of 9.6 g/dL was used here, the mean Hb concentration before transfusion in this study was 8.2 g/dL, which is considerably lower. In contrast with thresholds for platelet transfusions, there are no prospective comparative trials that have established the optimal Hb concentration in this specific patient group. However, the transfusions have been carried out according to current clinical standards in the Netherlands and, therefore, we chose to use this threshold. We expect that the slight (but highly consistent) increase in StO_2 and THI levels observed in this study will be more extensive when a lower transfusion threshold is applied.

In conclusion, we demonstrated that, although anemia in chronically anemic hematology outpatients was not associated with low StO_2 and THI levels, RBC transfusions were successful in increasing the values associated with these variables. We also showed that the chronic nature of anemia is not the limiting factor in the efficacy of RBC transfusions at the microcirculatory level in some anemic patient groups.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this work.

REFERENCES

1. Sakr Y, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, Creteur J, Gullo A, Vincent JL, De Backer D. Microvascular response to red blood cell transfusion in patients with severe sepsis. Crit Care Med 2007;35:1639-44.
2. Creteur J, Neves AP, Vincent JL. Near-infrared spectroscopy technique to evaluate the effects of red blood cell transfusion on tissue oxygenation. Crit Care 2009;13 Suppl 5:S11.
3. Yuruk K, Almac E, Bezemer R, Goedhart P, de Mol B, Ince C. Blood transfusions recruit the microcirculation during cardiac surgery. Transfusion 2011;51:961-7.
4. Ince C. The microcirculation is the motor of sepsis. Crit Care 2005;9 Suppl 4:S13-9.
5. Rossi EC. Red cell transfusion therapy in chronic anemia. Hematol Oncol Clin North Am 1994;8:1045-52.
6. Van Rhenen DJ, Haas FJ, De Vries RR, editors. Transfusiegids. 2011 (CBO guidelines, p. 21 and p. 117).
7. Sanquin Blood Supply Foundation. Sanquin website (Dutch blood bank). [cited 2011 Jun 10]. Available from:

URL: http://sanquin.nl/Sanquin-eng/sqn_products_Blood.nsf/All/Erythrocytes.html
8. Bezemer R, Lima A, Myers D, Klijn E, Heger M, Goedhart PT, Bakker J, Ince C. Assessment of tissue oxygen saturation during a vascular occlusion test using near-infrared spectroscopy: the role of probe spacing and measurement site studied in healthy volunteers. Crit Care 2009;13 Suppl 5:S4.
9. Myers DE, Anderson LD, Seifert RP, Ortner JP, Cooper CE, Beilman GJ, Mowlem JD. Noninvasive method for measuring local hemoglobin oxygen saturation in tissue using wide gap second derivative near-infrared spectroscopy. J Biomed Opt 2005;10:034017.
10. Cui W, Kumar C, Chance B. Experimental study of migration depth for the photons measured at sample surface. Proc SPIE 1991;1431:180-91.
11. Chance B, Dait MT, Zhang C, Hamaoka T, Hagerman F. Recovery from exercise-induced desaturation in the quadriceps muscles of elite competitive rowers. Am J Physiol 1992;262:C766-75.
12. Myers D, McGraw M, George M, Mulier K, Beilman G. Tissue hemoglobin index: a non-invasive optical measure of total tissue hemoglobin. Crit Care 2009;13 Suppl 5:S2.
13. Mutsaerts HJ, Out M, Goedhart PT, Ince C, Hardeman MR, Romijn JA, Rabelink TJ, Reiber JH, Box FM. Improved viscosity modeling in patients with type 2 diabetes mellitus by accounting for enhanced red blood cell aggregation tendency. Clin Hemorheol Microcirc 2010;44:303-13.
14. Corwin HL. Anemia and blood transfusion in the critically ill patient: role of erythropoietin. Crit Care 2004;8 Suppl 2: S42-4.
15. Raat NJ, Verhoeven AJ, Mik EG, Gouwerok CW, Verhaar R, Goedhart PT, de Korte D, Ince C. The effect of storage time of human red cells on intestinal microcirculatory oxygenation in a rat isovolemic exchange model. Crit Care Med 2005;33:39-45; discussion 238-9.
16. Koch CG, Li L, Van Wagoner DR, Duncan AI, Gillinov AM, Blackstone EH. Red cell transfusion is associated with an increased risk for postoperative atrial fibrillation. Ann Thorac Surg 2006;82:1747-56.
17. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499-507.
18. Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P. Are blood transfusions associated with greater mortality rates? Results of the sepsis occurrence in acutely ill patients study. Anesthesiology 2008;108:31-9.
19. Tuinman PR, Vlaar AP, Cornet AD, Hofstra JJ, Levi M, Meijers JC, Beishuizen A, Groeneveld AJ, Juffermans NP. Blood transfusion during cardiac surgery is associated with inflammation and coagulation in the lung: a case control study. Crit Care 2011;15:R59.
20. Lenz C, Rebel A, Waschke KF, Koehler RC, Frietsch T. Blood viscosity modulates tissue perfusion: sometimes and somewhere. Transfus Altern Transfus Med 2008;9:265-72.
21. Genzel-Boroviczeny O, Christ F, Glas V. Blood transfusion increases functional capillary density in the skin of anemic preterm infants. Pediatr Res 2004;56:751-5.
22. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. Intensive Care Med 2010;36:1286-98.
23. Bartels SA, Bezemer R, de Vries FJ, Milstein DM, Lima A, Cherpanath TG, van den Meiracker AH, van Bommel J, Heger M, Karemaker JM, Ince C. Multi-site and multi-depth near-infrared spectroscopy in a model of simulated (central) hypovolemia: lower body negative pressure. Intensive Care Med 2011;37:671-7.
24. Dani C, Pratesi S, Fontanelli G, Barp J, Bertini G. Blood transfusions increase cerebral, splanchnic, and renal oxygenation in anemic preterm infants. Transfusion 2010;50: 1220-6.
25. Cohn SM, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Beilman GJ. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. J Trauma 2007;62:44-54; discussion -5.
26. Crookes BA, Cohn SM, Bloch S, Amortegui J, Manning R, Li P, Proctor MS, Hallal A, Blackbourne LH, Benjamin R, Soffer D, Habib F, Schulman CI, Duncan R, Proctor KG. Can near-infrared spectroscopy identify the severity of shock in trauma patients? J Trauma 2005;58:806-13; discussion 13-6.
27. Jeger V, Jakob SM, Fontana S, Wolf M, Zimmermann H, Exadaktylos AK. 500 mL of blood loss does not decrease non-invasive tissue oxygen saturation (StO_2) as measured by near infrared spectroscopy—A hypothesis generating pilot study in healthy adult women. J Trauma Manag Outcomes 2010;4:5.
28. Creteur J, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL. The prognostic value of muscle StO_2 in septic patients. Intensive Care Med 2007;33:1549-56.
29. De Blasi RA, Palmisani S, Alampi D, Mercieri M, Romano R, Collini S, Pinto G. Microvascular dysfunction and skeletal muscle oxygenation assessed by phase-modulation near-infrared spectroscopy in patients with septic shock. Intensive Care Med 2005;31:1661-8.
30. Pareznik R, Knezevic R, Voga G, Podbregar M. Changes in muscle tissue oxygenation during stagnant ischemia in septic patients. Intensive Care Med 2006;32:87-92.
31. Doerschug KC, Delsing AS, Schmidt GA, Haynes WG. Impairments in microvascular reactivity are related to organ failure in human sepsis. Am J Physiol Heart Circ Physiol 2007;293:H1065-71.

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REFERENCES

1. Kaushansky K, Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Prchal JT, editors. Williams hematology. 8th ed. New York: McGraw-Hill Companies, Inc.; 2010.
2. Klein HG, Anstee DJ, editors. Mollison's blood transfusion in clinical medicine. 11th ed. Malden (MA): Blackwell Publishing; 2005.
3. Roback JD, Combs MR, Grossman BJ, Hillyer CD, editors. Technical manual. 16th ed. Bethesda (MD): American Association of Blood Banks; 2008.
4. Simon TL, Snyder EL, Stowell CP, Strauss RG, Solheim BG, Petrides M, editors. Rossi's principals of transfusion medicine. 4th ed. Bethesda (MD): Wiley-Blackwell; 2009.
5. Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. Authored by the TRAP Study Group, J. McCullough participant. N Engl J Med 1997;337:1861-9.

Blood transfusion and the microcirculation

We applaud the recent paper by Yuruk and colleagues[1] for emphasizing the importance of microcirculatory oxygen delivery and uptake when determining effects of allogeneic blood transfusion. While the authors demonstrated that transfusion improved the systemic circulation and oxygen-carrying capacity, improved microcirculatory density, and caused an increase in the microcirculatory oxygen saturation, we feel that these results should not necessarily be generalized to most clinical transfusions because the microcirculation during nonpulsatile, hypothermic perfusion on cardiopulmonary bypass is unique and is unlikely to represent the "typical" microcirculatory environment of most transfusion recipients. Additionally, the microcirculatory response to transfusion is likely to vary with the underlying clinical pathology (shock, sepsis, etc.) and other factors, including the age of the stored blood. Moreover, the authors provided no information on changes in oxygen delivery and uptake that occur in the microcirculation during cardiopulmonary bypass without transfusion.

The results of this study seem to be in conflict with animal studies showing a relative lack of improvement in microcirculatory oxygen delivery and uptake from stored blood transfusion.[2,3] We would appreciate the authors' evaluation of their findings in light of these studies.

CONFLICT OF INTEREST

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REFERENCES

1. Yuruk K, Almac E, Bezemer R, Goedhart P, de Mol B, Ince C. Blood transfusions recruit the microcirculation during cardiac surgery. Transfusion 2011;51:961-7.
2. van Bommel J, de Korte D, Lind A, Siegemund M, Trouwborst A, Verhoeven AJ, Ince C, Henny CP. The effect of the transfusion of stored RBCs on intestinal microvascular oxygenation in the rat. Transfusion 2001;41:1515-23.
3. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 2004;44: 1626-34.