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

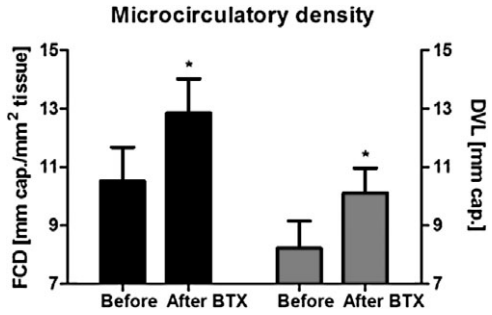

Fig. 1. Microcirculatory density, expressed as FCD (mm capillary [cap.]/mm² tissue) and DVL (mm capillary [cap.]), before and 30 minutes after blood transfusion (BTX). *p < 0.05 for before versus after BTX.

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

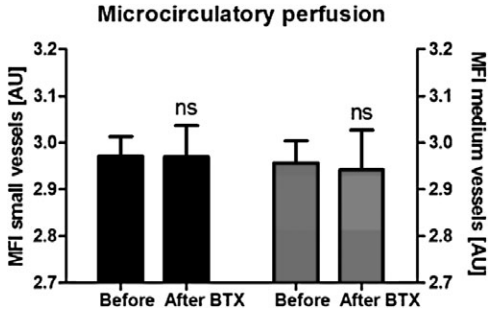

Fig. 2. Microcirculatory perfusion, expressed in MFI (AU), in small- and medium-sized vessels before and 30 minutes after blood transfusion (BTX). ns = not significant.

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.

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