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IMPACT OF RED BLOOD CELL TRANSFUSION ON GLOBAL AND REGIONAL MEASURES OF OXYGENATION

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Abstract

Anemia is common in critically ill patients. While the goal of transfusion of red blood cells (RBCs) is to increase oxygen carrying capacity, there are contradictory results about whether RBC transfusion to treat moderate anemia (e.g. hemoglobin 7–10 g/dL) improves tissue oxygenation or changes outcomes. While increasing levels of anemia eventually lead to a level of critical oxygen delivery (DO_2), increased cardiac output and oxygen extraction are homeostatic mechanisms the body uses to prevent a state of dysoxia in the setting of diminished DO_2 due to anemia. In order for cardiac output to increase in the face of anemia, normovolemia must be maintained. Transfusion of RBCs increases blood viscosity which may actually decrease cardiac output (barring a state of hypovolemia prior to transfusion). Studies have generally shown that transfusion of RBCs fails to increase oxygen uptake (VO_2) unless VO_2/DO_2 dependency exists, e.g., severe anemia or strenuous exercise. Recently near-infrared spectroscopy (NIRS), which approximates the hemoglobin saturation of venous blood, has been used to investigate whether transfusion of RBCs increases NIRS measurements of tissue oxygenation in regional tissue beds (e.g., brain, peripheral skeletal muscle). These studies have generally shown increases in NIRS derived measurements of tissue oxygenation following transfusion. Studies evaluating the effect of transfusion on the microcirculation have shown that transfusion increases the functional capillary density. This article will review fundamental aspects of oxygen delivery and extraction, and the effects of RBC transfusion on tissue oxygenation as well as the effects of RBC transfusion on the microcirculation.

Keywords

anemia; packed red blood cell (PRBC) transfusion; tissue oxygenation; oxygen uptake and delivery; near-infrared spectroscopy (NIRS); video microscopy; microcirculation

Transfusion of packed red blood cells (PRBCs), one of the most common medical interventions, is used to treat anemia to avoid the deleterious consequences of impaired tissue oxygenation, especially in settings of hemorrhage and shock. While it is likely that transfusion improves oxygenation and outcome in severe life-threatening anemia, it is unclear to what extent tissue oxygenation or outcome is improved in patients with moderate anemia (e.g., hemoglobin 7–10 g/dL), which is the clinically relevant range for much of the existing controversy. This review will summarize oxygen delivery and extraction, anemia, and the effects of PRBC transfusion on tissue oxygenation in humans as well as the effects of PRBC transfusion on the microcirculation.

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OXYGEN DELIVERY AND EXTRACTION

Understanding the potential impact of transfusion of RBCs on tissue oxygenation requires a review of the basic physiology of oxygen delivery and uptake and the concept of critical oxygen delivery. Oxygen delivery (ml/min) is defined as $DO_2 = Q \times CaO_2 \times 10$ where Q is cardiac output and CaO_2 is the arterial O_2 content defined as $(1.34 \times \text{hemoglobin concentration} \times SaO_2) + (0.003 \times PaO_2)$. The term $0.003 \times PaO_2$ accounts for the amount of dissolved oxygen in the blood. The venous O_2 content, CvO_2 , is analogous to the equation for the arterial O_2 content, but the mixed venous saturation and partial pressure of oxygen in venous blood, the SvO_2 and PvO_2 respectively, are replaced for the SaO_2 and PaO_2 . Thus oxygen delivery is partially dependent on the hemoglobin concentration and the arterial hemoglobin oxygen saturation; cardiac output is also an important determinant of DO_2 .

The rate at which oxygen dissociates from hemoglobin in the microcirculation and moves into the tissues is known as oxygen uptake (VO_2). As with oxygen delivery, it is expressed in ml/min and since oxygen is used in the tissues as it is released from hemoglobin, oxygen uptake is synonymous with oxygen consumption. Oxygen uptake is defined mathematically as $VO_2 = Q \times 13.4 \times \text{hemoglobin concentration} \times (SaO_2 - SvO_2)$ and calculating oxygen uptake in this manner is known as the reverse Fick method. The VO_2 can also be measured directly, but the pros and cons of these two different methods of calculating the VO_2 are beyond the scope of this review.

The ratio of oxygen uptake to delivery is known as the oxygen-extraction ratio and this value is normally approximately 0.25, although it can increase to minimize the risk of anaerobic metabolism if oxygen delivery is decreased. The lowest oxygen delivery that still supports aerobic metabolism is known as the critical oxygen delivery, but since it is not possible to predict the critical oxygen delivery in any given patient this parameter has not been clinically useful (1).

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ANEMIA

Barring impairment in hemoglobin function (e.g., hemoglobinopathy, carbon monoxide poisoning etc.), anemia is present when there is a decreased circulating red blood cell (RBC) mass. While simultaneous calculation of total RBC mass and plasma volume is possible using radiolabeled erythrocytes and plasma (2), it is generally not practical to use this test clinically, although newer techniques that produce more rapid results may gain more widespread acceptance (3). Thus the decision to transfuse PRBCs is not usually based on a documented deficiency of RBC mass, but rather is typically heavily influenced by the hemoglobin or hematocrit value. While these values do have some relationship with the total RBC mass, they do not consider the plasma volume and in hospitalized patients deemed in need of a PRBC transfusion, accurately estimating the plasma volume is not trivial. Estimating the plasma volume is even more difficult in patients with acute hemorrhage. While it is axiomatic that the hematocrit is unreliable in the setting of acute hemorrhage, it is still a point worth reemphasizing. Moreover because acute hemorrhage results in loss of whole blood, prior to resuscitation the hematocrit will overestimate the RBC mass and

following resuscitation, the hematocrit more accurately reflects the fluid used for resuscitation rather than the RBC mass(1). In any case transfusion of PRBCs is indicated empirically for trauma patients who remain in shock following infusion of 2 liters of crystalloid (4).

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As CaO_2 falls with anemia, DO_2 is maintained by increased cardiac output assuming normal coronary artery reserve (5). Additionally, stable tissue oxygenation is maintained with mild to moderate levels of anemia as peripheral tissues increase oxygen extraction by altering microvascular blood flow (6). In conditions of severe hemodilution (isovolemic anemia), microvascular function is impaired because the functional capillary density (FCD) is diminished. Below a threshold FCD, Kerger *et al.* found decreased survival in a model of extended hemorrhagic shock (7). FCD can be maintained in this setting with infusion of high viscosity plasma expanders or with transfusion of PRBCs. Importantly, the viscosity below which the FCD decreases seems to correlate with the hemoglobin level that results in critical oxygen delivery (8). Therefore, normal physiologic mechanisms (i.e. increased cardiac output and oxygen extraction) allow patients without significant comorbidities to tolerate even severe anemia, as long as isovolemia is maintained, perhaps even given the microvascular dysfunction that can occur with severe anemia as described above.

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A recent case report demonstrates an extreme example of this maxim. A 53 year-old man in China with no past medical history sustained a severe hemorrhage following injury to the axillary artery. Due to the lack of availability of cross-matched or type-O negative blood, the patient was severely anemic for almost the entire duration of a 12 hour surgical procedure to repair his neurovascular injuries. Remarkably, the patient's preoperative hemoglobin concentration was 0.9 g/dl and the nadir hemoglobin intraoperatively was 0.7 g/dl. Intravascular volume was maintained, metabolic acidosis was treated with sodium bicarbonate, and the patient's lungs were ventilated with 100% oxygen during the surgical procedure. No vasoconstrictors or inotropes were administered. Cross-matched blood became available towards the end of surgery and transfusion of PRBCs was started at that point. Intraoperatively the patient showed no signs of myocardial ischemia and post-operatively he demonstrated no neurocognitive deficits (9).

This case report, and others involving Jehovah's Witness patients, demonstrate that even severe anemia will generally not compromise tissue oxygenation in an isovolemic patient. However, it should be emphasized that in anemic patients with comorbidities, e.g., coronary artery disease, arterial oxygen content and global oxygen delivery may be adequate but due to limitations in regional perfusion, oxygen delivery to a specific organ, e.g., the myocardium, may be inadequate. This issue makes it more difficult for the clinician to predict what level of anemia is clinically significant in a specific patient. Because both anemia and hypovolemia can interfere with oxygen transport (10), it is important for the clinician to treat the underlying etiology of impaired oxygen transport rather than reflexively transfusing PRBCs to a hypovolemic patient, unless the patient has hemorrhagic shock. Thus hypovolemia should generally be treated with crystalloid or colloid administration and

PRBCs should be reserved for patients with anemia. In the setting of hemorrhagic shock, PRBCs are given empirically if shock does not respond to 2 liters of crystalloid given the high index of suspicion for anemia in this setting (4).

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METHODS OF INCREASING OXYGEN DELIVERY

Oxygen delivery can be increased by raising the inspired concentration of oxygen to produce a supranormal PaO_2 , as described above (9). While the amount of oxygen dissolved in the blood is normally trivial compared with amount carried by hemoglobin, under conditions of severe anemia with a PaO_2 greater than 400 mm Hg, the amount of dissolved oxygen has been estimated to be equivalent to 3 g/dl of hemoglobin (11, 12). Oxygen delivery can also be increased by increasing cardiac output through use of inotropes or fluid administration. A full discussion of this topic is beyond the scope of this review.

In anemic patients, transfusion of PRBCs to increase the hemoglobin concentration is a common maneuver to increase oxygen delivery. However, there are several physiological and theoretical issues which could limit the beneficial effects of transfusion on oxygen delivery. For example, transfusion of PRBCs increases blood viscosity which can decrease cardiac output (13), assuming that cardiac output is not impaired by myocardial ischemia from critical oxygen delivery. The decreased cardiac output that can result from transfusion of PRBCs may counteract the goal of improving oxygen delivery by increasing the hemoglobin concentration, although in certain situations decreasing the cardiac output may be beneficial. In the setting of severe anemia, increasing blood viscosity can actually help recruit the microcirculation by maintaining or recruiting the FCD as described above (8). Also despite the increase in blood viscosity induced by transfusion of PRBCs, in a hypovolemic patient, administration of PRBCs will generally increase cardiac output due to the volume effect of this colloid. As a general rule, cardiac output increases in the following order after infusion of fluid: asanguineous colloid > whole blood > lactated ringers > PRBCs (14). The relative merits of using crystalloid versus colloid for correction of hypovolemia are beyond the scope of this review.

Another potential limitation of PRBC transfusion relates to known biochemical changes in RBCs during storage, known collectively as the “storage lesion” (15). For example, 2–3,DPG, which promotes off-loading of oxygen from hemoglobin in tissues, is depleted as early as 14 days into the 42 day allowed period of storage (15). Decreased deformability of RBCs in stored blood could theoretically be detrimental to microcirculatory flow and oxygen delivery. For example, in animal studies transfusion of stored, but not fresh PRBCs, impaired flow through the microcirculation and tissue oxygenation (16, 17). However, other animal studies have shown that transfusion of PRBCs, fresh or old, recruited the microcirculation by recruiting FCD, at least in the setting of extreme anemia from hemodilution (8). Whether transfusion of PRBCs stored for longer periods of time causes complications is controversial (18), although studies to this point are hampered by their observational and retrospective designs. To address shortcomings of previous trial designs on this issue, three multicenter randomized controlled trials designed to test whether transfusion of shorter stored PRBCs results in improved outcomes are underway (19–21).

While it is attractive to believe that transfusion should be beneficial to anemic patients, there are several theoretical reasons why this may not be the case. Indeed, as described below there is a glaring lack of evidence to support the hypothesis that PRBC transfusion has clinically beneficial effects on tissue oxygenation and outcome.

IMPACT OF RED BLOOD CELL TRANSFUSION ON GLOBAL MEASURES OF OXYGEN DELIVERY AND CONSUMPTION

Napolitano *et al.* recently reviewed PRBC transfusion in adult trauma and critical care and concluded that PRBC transfusion should not be considered a reliable method of improving oxygen uptake in critically ill patients (10) based on 21 human studies evaluating the effect of PRBC transfusion on DO_2 and VO_2 (see table 5 in clinical practice guideline by Napolitano *et al.*). In these studies, DO_2 generally increased following transfusion, but VO_2 increased in only three of the studies (10). While these studies measured global oxygen delivery and uptake rather than tissue oxygenation, collectively these results argue against an increase in tissue oxygenation unless it only occurs in select tissue beds. Additionally, of the 21 studies cited by Napolitano *et al.*, only four were published following the publication of the landmark TRICC trial (22). The TRICC trial, which randomized 838 critically ill patients to liberal (goal hemoglobin 10–12 g/dL) versus restrictive (goal hemoglobin 7–9 g/dL) transfusion strategies, observed no benefit to liberal transfusion. Indeed, the study almost achieved ($p=0.11$) statistical significance for a finding of increased mortality in patients randomized to liberal transfusion. Unfortunately, these compelling findings from the late 1990s have to date not been confirmed.

It should also be noted that while Napolitano *et al.* cite numerous studies demonstrating the failure of PRBCs to increase VO_2 , it is possible that the higher transfusion threshold generally used in these studies masked the potential of transfused PRBCs to increase VO_2 (23). In other words, these studies do not address the question of whether PRBC transfusion improves oxygenation and outcome in patients with severe anemia, (e.g., hemoglobin of 4 g/dL). However, it should be noted that Napolitano *et al.* cite level 1 evidence that RBC transfusion is indicated in patients with hemorrhagic shock (12). Additionally while PRBC transfusion may not increase the VO_2 in circumstances where VO_2/DO_2 dependency does not exist, transfusion can have other effects that may be beneficial in certain situations such as an increase in the FCD, changes in cardiac output, and an increased oxygen reserve.

IMPACT OF RBC TRANSFUSION ON REGIONAL MEASURES OF TISSUE OXYGENATION AND THE MICROCIRCULATION

A limitation of the previous studies is that they largely focused on the effects of transfusion on global measures of oxygen delivery and consumption. Invasive methods for measuring tissue oxygenation in research studies have been reported (24), but most are generally not appropriate for routine clinical use. Near-infrared spectroscopy (NIRS) technology has recently become available as a non-invasive FDA approved tool to measure tissue oxygenation in a variety of end-organ tissue beds; muscle in the thenar eminence and brain tissue are the two sites most commonly monitored. NIRS uses near-infrared light to measure oxyhemoglobin and deoxyhemoglobin, the fractions of which are used to calculate the tissue oxygen saturation; however the near-infrared light also captures absorbance from myoglobin and cytochrome aa3 (25). When NIRS is used to measure the tissue oxygenation of the peripheral muscle (where it is known as the StO_2) the infrared light can only obtain data from small vessels (arterioles, capillaries, and venules) and because 75% of the blood in skeletal muscle is venous, NIRS values mostly reflect the venous blood hemoglobin saturation (25). NIRS values therefore are thought to be an approximate measure of the

hemoglobin saturation of blood following oxygen extraction in any particular tissue. NIRS technology and its potential benefit in surgery were recently reviewed by Cohn (26).

Because NIRS can be used to approximate the hemoglobin saturation of venous blood, numerous studies have investigated whether transfusion of PRBCs increases NIRS measurements of tissue oxygenation. A number of studies have shown that tissue oxygenation measured by NIRS increases following transfusion of PRBCs. A recent study assessing the effect of transfusion of an average of three units of PRBCs (average age of 21 days) to anemic, hematology outpatients found a significant increase in thenar and sublingual StO_2 (data presented as median (25–75%); thenar StO_2 81% (80–84%) pretransfusion to 86% (81–89%) after transfusion ($p=0.002$); sublingual StO_2 86% (81–89%) pretransfusion to 91% (86–92%) after transfusion ($p<0.0001$), despite the fact that these anemic patients had StO_2 values that were normal prior to transfusion (27). Another observational study of 29 patients transfused PRBCs intraoperatively and monitored with cerebral oximetry found that the cerebral oxygen saturation increased by a mean (95% CI) of 4.2% (3.2–5.2%; $p=0.001$) following transfusion, although the SpO_2 also increased by 1.6% (0.3–2.8%; $p=0.016$) following transfusion (28). A number of studies using NIRS in a pediatric population have also shown that tissue oxygenation increases following transfusion of PRBCs. Van Hoften *et al.* performed a prospective, observational, cohort study in anemic, preterm infants to study whether the cerebral tissue oxygen saturation (ScO_2) measured with NIRS and fractional tissue oxygen extraction (FTOE, defined as $([\text{SpO}_2 - \text{ScO}_2]/\text{SpO}_2)$) were associated with the hemoglobin concentration before and after transfusion of PRBCs. ScO_2 and FTOE were strongly correlated with hemoglobin concentration before transfusion ($r=0.414$ and $r=-0.462$, respectively, $p<0.005$). Twenty-four hours after transfusion, ScO_2 increased from a weighted mean of 61% to 72% and FTOE decreased from a weighted mean of 0.34 to 0.23. These changes were most pronounced in the group with a hemoglobin concentration below 9.7 g/dl suggesting that cerebral oxygenation in preterm infants may be at risk when the hemoglobin concentration decreases below 9.7 g/dl (29). In an observational study designed to assess the response of tissue oxygenation to PRBC transfusion in 15 anemic, preterm infants transfused for symptomatic anemic of prematurity (hematocrit $< 25\%$), transfusion was shown to significantly increase regional (brain, splanchnic, and renal) tissue oxygenation measured with NIRS and decrease the oxygen extraction ratio in these tissue beds (30).

In another prospective, observational study NIRS was used to monitor changes in tissue oxygenation of the lower leg during blood transfusion in hemodynamically stable, anemic, preterm infants. The oxygenation extraction index (OEI) was calculated before and after transfusion from NIRS derived data. The OEI decreased from a pre-transfusion value of 0.31 to 0.24 ($p<0.005$) following transfusion of 10–20 ml/kg of PRBCs. This decrease was positively correlated with the weight matched amount of PRBCs transfused ($r^2=0.40$, $p<0.05$) and with the increase in hematocrit ($r^2=0.58$, $p<0.005$) following transfusion (31). Finally, Bailey *et al.* conducted a prospective, observational study in 30 symptomatically anemic, preterm infants requiring transfusion of PRBCs to assess the ability of NIRS to show an increase in tissue oxygenation following transfusion. They found a statistically significant increase in both the cerebral tissue oxygenation (CrSO_2) and the splanchnic tissue oxygenation (SrSO_2) values during transfusion, immediately after transfusion, and 12 hours after transfusion compared with the pre-transfusion value. For CrSO_2 the NIRS data for pre-transfusion, during transfusion, immediately post-transfusion, and 12 hours post-transfusion were: 62.8 ± 1.6 , 65.6 ± 1.7 , 68.0 ± 1.3 , 67.6 ± 1.4 , $P < 0.001$ and for SrSO_2 they were: 41.3 ± 2.2 , 46.7 ± 3.0 , 52.1 ± 2.8 , 48.2 ± 2.5 , $p < 0.001$ (32).

Other studies, using tools other than NIRS, have also shown that transfusion of PRBCs increases tissue oxygenation. Many of these have measured tissue oxygenation in the brain

or used surrogates of this measurement. Figaji *et al.* performed a retrospective analysis of children with severe traumatic brain injury (TBI) who had brain tissue oxygen tension (PtiO₂) monitoring with a Clarke type oxygen electrode and received a blood transfusion to examine the influence of PRBC transfusion on PtiO₂. They found that PtiO₂ increased significantly in the period following transfusion of PRBCs in children with TBI. However, 24 hours following transfusion there was no longer a significant increase in PtiO₂ (33).

Another prospective, observational study, in anemic patients with subarachnoid hemorrhage or traumatic brain injury who required transfusion of PRBCs and monitoring of local brain tissue oxygen partial pressure (PbtO₂), found that PbtO₂ increased in 74% of transfused patients. The mean±SD increase in PbtO₂ for all patients was 3.2±8 mm Hg (p=0.02), a 15% increase from the value one-hour prior to transfusion. Changes in PbtO₂ were independent of changes in cerebral perfusion pressure, arterial oxygen saturation, or the inspired oxygen concentration with mechanical ventilation (34). Because urinary oxygen tension (P(u)O₂) is a potential marker of renal blood flow and tissue oxygenation, Valente *et al.* conducted an observational study of the response of P(u)O₂ to transfusion of PRBCs in anemic patients undergoing surgical procedures. They found that PRBC transfusion resulted in a significant increase in P(u)O₂ measured by co-oximetry; mean±SD pre- and post-transfusion urinary oxygen tension was 90±14 and 108±20 mmHg, respectively (p=0.036) (35).

Weiskopf *et al.* reported a human model of isovolemic anemia (5–6 g/dl) in which cognitive function becomes oxygen dependent (11, 36, 37) and showed that fresh autologous blood (< 5 hours old) was as effective as stored autologous blood (3 weeks old) at reversing the neurocognitive deficit in performing the digit–symbol substitution test that develops with acute anemia (38). While cerebral oximetry was not used to measure brain tissue oxygenation in the experiments performed by Weiskopf *et al.*, the strength of this model is that it is used a functional assessment of human cognitive performance.

Transfusion of PRBCs is common in cardiac surgery (39) and there have been several studies assessing the impact of transfusion on tissue oxygenation in cardiac surgery. An observational study of anemic patients transfused PRBCs in cardiac surgery showed that the oxygen extraction ratio, (O₂ER, a measure of oxygen uptake at the level of the microcirculation defined as the ratio of VO₂/DO₂) fell significantly following transfusion of PRBCs only in patients whose pre-transfusion O₂ER was increased. In this study an increased O₂ER was defined as greater than 30%, an intentionally conservative cutoff rather than the more typical 50% cutoff for O₂ER, which is considered to be indicative of globally inadequate tissue oxygenation (40). Because this was an observational study it does not prove that withholding transfusion in anemic patients until the O₂ER ratio surpasses a predetermined value would be a safe and effective method of deciding when a patient needed a transfusion, but it is an interesting idea worthy of further study in patients who have an indwelling pulmonary artery catheter. Also, it suggests that transfusion augments tissue oxygenation in patients at risk for tissue hypoxia (i.e. O₂ER > 30%) but not in patients with an O₂ER < 30%.

In another prospective, observational study in patients undergoing cardiac surgery with cardiopulmonary bypass, sublingual spectrophotometry of the microcirculation before and after transfusion of PRBCs was measured. Transfusion of PRBCs increased the microcirculatory hemoglobin content (61.4 ± 5.9 to 70.0 ± 4.7 absorbance units, p<0.01) and showed a trend towards increasing the microcirculatory hemoglobin oxygen saturation (65.6 ± 8.3% to 68.6 ± 8.4%, p=0.06) (41).

Two recent studies, however, have shown no change in tissue oxygenation as measured by NIRS following transfusion. In one prospective, observational study in critically ill anemic

patients, transfusion of PRBCs did not increase muscle tissue oxygenation based on NIRS measurements (42). Muscle oxygen consumption, also assessed by NIRS, was unaltered unless it was low prior to transfusion (42). In a second study, also in the critically ill, anemic trauma patients transfused with PRBCs did not show an increase in NIRS measurements of muscle tissue oxygenation, and transfusion of old PRBCs (> 21 days old) actually resulted in a statistically significant decrease in tissue oxygenation, although the absolute decrease in tissue oxygenation was small (43).

Sidestream darkfield (SDF) and orthogonal polarization spectral (OPS) are two bedside video microscopy techniques that produce real-time images of RBCs in the microcirculation. These techniques are typically used to produce sublingual images, although it is possible to record images from other mucosal sites. Importantly SDF/OPS video microscopy do not visualize the vessel wall, so only vessels containing RBCs are imaged and in the sublingual area the arterioles are typically too deep to visualize, so capillaries and venules are the vessels seen with this technique. These video microscopy techniques can be used to estimate heterogeneity of perfusion and capillary density, variables that are relevant to tissue perfusion, using semi-quantitative analysis with good inter-rater reliability (25). In a study using OPS to evaluate the effect of PRBC transfusion in anemic, pre-term infants, functional capillary density (FCD) was found to increase significantly at 2 and 24 hours following transfusion [pre-transfusion: 142 (134–155); 2 hours after transfusion: 185 (166–196); 24 hours after transfusion: 206 (185–219) cm/cm²; $p < 0.001$], indicating improved microvascular perfusion (44). In an observational study assessing the influence of PRBC transfusion on the sublingual microcirculation of anemic patients with severe sepsis, Sakr *et al.* found no significant difference in microvascular perfusion (using OPS) one-hour after transfusion. Capillary perfusion did increase by > 8% in patients whose capillary perfusion was significantly lower at baseline (57 [52–64] versus 75 [70–79]; $p < 0.01$) highlighting the importance of the pre-transfusion physiology on the response to transfusion (45).

Many studies of the studies on the effect of PRBC transfusion on the microcirculation have been done in animal models using the rat cremaster muscle flap model or the hamster window chamber model using intravital microscopy, which is the classic technique in animal models. The data from intravital microscopy is similar to that generated by OPS/SDF, although the two types of techniques have not been validated against one another (25). In a preliminary study comparing the effect of fresh versus stored whole blood transfusion on microcirculatory flow parameters following hemorrhage in the rat cremaster muscle flap model, Arslan *et al.* found that fresh blood was significantly more effective than banked blood at restoring the deficit in functional capillary perfusion created by acute hemorrhage (46). In a larger study using the same model, this group again found that functional capillary perfusion was more effectively restored by fresh whole blood following hemorrhage compared with stored blood (47). Additionally they found that transfusion of fresh whole blood restored the microcirculatory tissue oxygenation to baseline levels while transfusion of stored whole blood did not (9.5 mm Hg versus 8 mm Hg, $p = 0.02$). Cabrales *et al.* found in the hamster window chamber model that transfusion of the equivalent of 2.5 units of PRBCs following 1 hour of untreated hemorrhagic shock restored blood viscosity more effectively than infusion of 10% hydroxyethyl starch (HES) and resulted in higher mean arterial blood pressures and FCD. Interestingly half of the transfused animals were transfused with fresh PRBCs where hemoglobin had been converted to methemoglobin to impair the RBCs ability to release oxygen in the microcirculation; as would be expected animals transfused with these PRBCs or resuscitated with 10% HES had lower oxygen delivery and extraction than animals transfused with fresh PRBCs (48).

CONCLUSION

There are conflicting data on whether transfusion of RPBCs increases tissue oxygenation. More importantly, there are few rigorously conducted randomized trials that have addressed this issue. The largest trial to date, TRICC (now more than a decade old) showed no survival benefit to liberal transfusion, and almost achieved statistical significance for improved survival in patients randomized to the lower transfusion trigger. It is critical to emphasize that, for ethical and pragmatic reasons, almost all previous studies limited their focus to transfusion in patients with “moderate” anemia, (i.e., hemoglobin greater than 6 or 7 g/dL). Therefore, the question of whether RBC transfusion improves oxygenation and outcome in patients with severe isovolemic anemia, (i.e., hemoglobin of 4 g/dL) is largely unanswered, although anecdotal evidence suggests that this is probably the case.

In the context of these conclusions it is worth reviewing the joint practice guidelines of the American College of Critical Care Medicine and the Eastern Association for Surgery of Trauma (10). These guidelines cite level 1 evidence that PRBC transfusion is indicated for patients with hemorrhagic shock and that using a restrictive transfusion strategy (Hb target of 7 g/dL) is safe in anemic patients who are hemodynamically stable, although a higher hemoglobin target may be necessary in patients with acute myocardial ischemia. These guidelines also extort clinicians to not focus exclusively on the hemoglobin concentration as a transfusion trigger. Instead they cite level 2 evidence that the transfusion of PRBCs should only occur after consideration of the patient’s volume status, whether there is evidence of shock, the duration and extent of the patient’s anemia, and the patient’s cardiorespiratory parameters (10). The failure of PRBC transfusion to improve tissue oxygenation is also mentioned in several places in these guidelines (10).

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