Review Article

Current practice optimization suggestions and future perspectives on transfusion in patients supported by extracorporeal membrane oxygenation: a narrative review

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Background and Objective: Patients on extracorporeal membrane oxygenation (ECMO) are transfused more than other critically ill patients. The risk of bleeding, anticoagulation, and restoration of oxygen carrying capacity are all reasons why practitioners decide to transfuse these patients. However, the cost/benefit ratio of transfusion in this setting is unclear, especially when practiced liberally. The association between the volume of red blood transfused and morbidity and mortality is becoming increasingly clearer. Therefore, more effort should be made to find transfusion-sparing strategies. This review explores studies on the practice of blood transfusion among ECMO patients, and whether a hemoglobin trigger is considered when deciding to transfuse. Furthermore, we wanted to identify alternative strategies for blood transfusion to maintain adequate oxygen delivery, such as optimal fluid balance, anticoagulation protocols, and dynamic ECMO configurations.

Methods: We used the PubMed database to identify articles on transfusion practice in ECMO patients and on possible strategies under development to improve patient blood management. All selected papers were written in English and published between 2003 and 2022.

Key Content and Findings: In this review we emphasize the importance of combining hemoglobin values with physiological parameters of peripheral perfusion to assess the need for transfusion. Optimizing blood flow dynamically with patient fluid balance and improving in ECMO circuit efficiency may also be important for meeting a patient's metabolic needs and sparing transfusion.

Conclusions: Clinical and research efforts should be made to optimize blood management of ECMO patients through a multidisciplinary approach.

Keywords: Extracorporeal membrane oxygenation (ECMO); transfusion; oxygenation; perspective

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Introduction

Background

Extracorporeal membrane oxygenation (ECMO) support has become the mainstay of cardiopulmonary replacement therapy in critically ill patients with terminal heart and/or lung disease (1). Its indications are becoming increasingly broader due to increased awareness and technological advances (2). Currently, ECMO support is undertaken for patients of varying age (from newborns to adults) and with different underlying conditions.

The ECMO population requires more transfusions

than other critically ill patients, and almost all ECMO patients are exposed to at least one blood product unit during support. The reasons for prompting practitioners to transfuse are multifactorial. ECMO leads to an increased risk of bleeding due to therapeutic cannulation, hemodilution, and activation of coagulation factors and cells. Priming volume leads to the hemodilution of almost all blood components, including coagulation factors and platelets. The extent of hemodilution depends on the patient's body surface area and the desired flow rate. Contact and shear stress between the blood column and the non-endothelial surface of the circuit leads to hemolysis and an inflammatory response. These can induce endothelial dysfunction and activation of the coagulation cascade and, potentially, consumptive coagulopathy. The absorption capacity of the artificial surface can contribute to the depletion of fibrinogen and other coagulation factors (3). Furthermore, as with all extracorporeal support, ECMO requires anticoagulants to avoid thrombosis of the patient's vessels, and clotting of the circuit.

During ECMO support, the negative pressure and turbulence generated by the pumps can lead to hemolysis, and hence anemia. Red blood cell (RBC) disruption releases factors that promote von Willebrand factor mediated-platelet adhesion and thrombosis (4). The cell-free plasma hemoglobin scavenges endothelial nitric oxide, limiting its bioavailability, leading to microvascular vasomotor dysregulation. Along with bleeding and hemolysis, anemia of chronic disease can contribute to reduced hemoglobin levels in patients on ECMO support. Therefore, practitioners are inclined to transfuse these patients to restore oxygen-carrying capacity and maintain adequate oxygen delivery (DO2).

Rationale and knowledge gap

Blood transfusions have a questionable cost-benefit ratio since they are expensive, and can increase morbidity and mortality. Packed red blood cells (PRBCs) are a risk-bearing therapy, particularly in high-acuity patients, such as those on ECMO. This special population has several intensive care unit (ICU)-related risk factors, including volume depletion or overload, infections, longer duration of mechanical ventilation, and longer length of ICU stay. All of these can contribute to development of such transfusion-related complications as acute lung injury, infections, fluid overload, and immunoreactions (5-7) that can precipitate the clinical conditions of these patients. Furthermore, prolonged storage of PRBCs can worsen hemolysis, and result in the release of free hemoglobin (fHb), which in turn causes the depletion of nitrogen oxides, and endothelial microvascular vasoconstriction (8).

To our knowledge, few prior studies have examined strategies to spare PRBC, such optimizing blood flow and fluid balance or dynamically changing ECMO configurations. However, advances in technology consistently impacted on transfusion requirements in patients on ECMO support. The most recent recommendations from the Extracorporeal Life Support Organization (ELSO) suggest maintaining hematocrit levels above 40% (which translates to hemoglobin levels above 13 g/dL) (9) to optimize oxygen delivery with the lowest reasonable blood circuit flow. Increasing expertise and bioengineering advances over the last 10 years have called these recommendations into question. In fact, modern ECMO circuits reduce the risk of bleeding and hemolysis (3,10). In addition, despite the severity of illness seen in the ECMO population, an increasing number of observational studies have shown the non-inferiority, in terms of morbidity and mortality, of a restrictive approach to transfusion practice with respect to liberal ones (11), as demonstrated in non-ECMO supported critically ill patients (12-15). In a recent systematic review and meta-analysis, the median transfusion threshold for both venovenous (VV) and venoarterial (VA) ECMO was 8 g/dL (12). In a recent Cochrane review, this transfusion threshold was shown not to increase mortality risk compared with higher thresholds (13).

Objective

This review examines the practice of blood transfusion in studies of ECMO patients and whether a hemoglobin trigger is considered when physicians decide to transfuse. In addition, we aimed to identify alternative blood transfusion strategies to maintain adequate oxygenation, such as optimal fluid balance, anticoagulation protocols, and dynamic ECMO configurations. We present this article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.org/article/view/10.21037/aob-23-11/rc).

Methods

The methods of our search are summarized in *Table 1*.

Table 1 The search strategy summary

Items	Specifications
Date of search	01/01/2023
Databases or other source searched	PubMed
Search terms used	"Extracorporeal membrane oxygenation", "ECMO", "packed red blood cells", "PRBC", "transfusion", "blood transfusion", "patient blood management", "transfusion requirements", "ECMO blood flow optimizations", "fluid balance and ECMO", "dynamic ECMO configuration"
Timeframe	2003–2022
Inclusion and exclusion criteria	Inclusion criteria: observational, randomized clinical trial, clinical trial, review, case report written in English
	Exclusion criteria: books, chapters or comment or articles written in a non-English language
Selection process	S.T. and P.C. conducted independently of the selection process. Consensus and revision was obtained by two senior authors (G.M. and F.S.)

ECMO, extracorporeal membrane oxygenation; PRBC, packed red blood cell.

Discussion

Transfusion practice in VV ECMO

Refractory respiratory failure during conventional therapy is the main indication for VV ECMO support. Oxygen uptake is the major issue in these patients, who generally maintain oxygen consumption in the normal range. In this setting, transfusing the patient does not further improve oxygen delivery despite an adequate oxygen uptake through an oxygenator, unless hemoglobin levels reach a critical point (14,15). Increasing oxygen extraction can allow oxygen uptake to remain stable until oxygen delivery falls below a critical level, as during severe anemia or hemorrhagic shock (16). There is still insufficient proof that increasing hemoglobin levels leads to increased oxygen delivery in the presence of oxygen extraction within normal range. When oxygen extraction is near 50%, it cannot increase in the presence of progressive anemia, and oxygen consumption tends to decrease simultaneously. A retrospective study investigated the relationship between transfusion practice and changes in perfusion markers, such as mixed venous saturation (SvO_2) and cerebral tissue oxygenation measured by near infrared spectroscopy (NIRS) (17). Most transfusions did not result in statistically significant changes in perfusion markers, revealing that they were administered when patients were in a non-dependent oxygen delivery state. It is possible that different practitioners transfuse patients in order to exploit the hemoglobin buffer effect in counteracting the oxygen diffusion deficit. However, futile RBC transfusion can limit the patient's oxygen delivery by different mechanisms: (I) an increase in hemoglobin oxygen affinity by depletion of 2–3 diphosphoglycerate (2–3 DPG) and adenosine-triphosphate (ATP) induced by long storage of RBCs (18); (II) an increase in blood viscosity and vascular resistance, leading to a potential decrease in cardiac output; (III) an increase in hemolysis and thrombosis events. In fact, PRBCs have increased osmolar fragility, and are prone to hemolysis (19), and free plasma hemoglobin can increase vascular resistance by depletion of endothelial NO (20).

The TRAIN-ECMO survey investigated transfusion practices among different centers in patients on VV ECMO compared with other critically ill patients, with a special emphasis on hemoglobin thresholds used to guide the transfusion therapy. The survey revealed a high variability in the Hb trigger in these centers, as shown in *Table 2*. Furthermore, patients on VV ECMO support are transfused at a higher Hb threshold compared with other critically ill patients, but this gap was narrower in higher volume centers (28). This high variability and the liberality in transfusion practice in VV ECMO patients is perhaps due to the lack of evidence on optimal transfusion triggers for hemoglobin values in this population (29). As a result, various observational studies (*Table 2*) have confirmed that patients receiving VV ECMO are highly transfused, with a prevalence approaching 100% (26,30-35), even in non-bleeding patients (36). However, a multicenter, prospective, cohort study reported a reduced PRBC transfusion percentage, likely due to advances in technologies and increased understanding of patient blood management (37).

Anticoagulation protocols can increase the risk of

Table 2 Observational studies on transfusion practice during VV ECMO support

Author/year (ref.)	Study type	Indication (surgical/non-surgical/mixed)	Indications	N	ECMO days (mean ± SD)	Transfusion trigger (g/dL)	PRBC/day (mean ± SD)	Survival to discharge (%)
Guirand 2014, (21)	Retrospective	Non-surgical	RF (trauma-associated ARDS)	26	9.3±9.5	NS	0.90±0.36	57.7
Lehle 2015, (8)	Retrospective	Non-surgical	RF	318	NS	8 g/dL	0.31±0.36	NS
Lewandowski 1997, (22)	Retrospective	Non-surgical	RF	49	23.1±19.7	15 g/dL	2.10±1.90	55.1
Panigada 2015, (23)	Prospective	Mixed	RF (ARDS/COPD/ bridge to LTx)	22	9.0±5.5	NS	0.97±1.09	NS
Trudzinski 2016, (24)	Retrospective	Non-surgical	RF (ARDS + COPD bridge to LTx)	63	22.4±17.4	7 g/dL	0.98±1.17	66.7
Voelker 2015, (25)	Retrospective	Non-surgical	RF	18	21.7±30.0	7 g/dL	1.35±1.16	61.1
Martucci 2019, (26)	Retrospective	Non-surgical	RF (ARDS)	82	14±10.4	8 g/dL	NS	77.8
Smith 2001, (27)	Retrospective	Non-surgical	RF (ARDS)	17	4.1±2.1	10 g/dL	7.21±3.13	41.2

VV ECMO, venovenous extracorporeal membrane oxygenation; SD, standard deviation; HCt, hematocrit; PRBC, packed red blood cell; RF, respiratory failure; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; LTx, lung transplantation; NS, not specified.

bleeding, and the need for blood products. In a monocentric prospective study, an anticoagulation protocol with only subcutaneous enoxaparin in prophylactic dosage, was found to obviate the need for blood products while achieving an adequate safely profile in 61 patients receiving VV ECMO and without a history of thrombosis (38). This finding should prompt clinicians to reconsider the ELSO recommendations to use therapeutic dosages of heparin in every patient on VV ECMO.

Several studies support the safety and feasibility of a restrictive transfusion strategy in VV ECMO patients. In a retrospective study, a hemoglobin trigger of 7 g/dL did not increase mortality in 18 patients undergoing VV ECMO for severe acute respiratory distress syndrome (ARDS) (25). Similarly, another retrospective study found that a gradual decrease in the hemoglobin threshold from 10 to 7 g/dL led to a reduced volume of blood transfused, without a significant clinical impact in patients on VV ECMO for severe ARDS (39). In a recent meta-analysis, a higher transfusion threshold was shown to be associated with increased mortality (12). For this reason and the above-mentioned transfusion-related complications, the decision to transfuse patients should be weighed considering not only absolute hemoglobin values, but the entire clinical picture (e.g., hemodynamic parameters, circuit change, bleeding). PRBC transfusions should be given when anemia becomes critical and affects the body's oxygen delivery (DO2) and coagulation status. In fact, if the patient's metabolic needs can be met with alternative treatments, such as adjusting Qec and optimizing fluid balance, the decision to transfuse may not be favorable for patient outcomes. In the PROTECMO study, an increased daily fluid balance led to increased mortality in ARDS patients supported with VV ECMO (37). Indeed, a more positive fluid balance exposes the patient to the risk of a non-beneficial high blood flow rate, with an increased risk of hemolysis and further PRBC transfusions. Furthermore, the authors concluded that PRBC transfusion increases survival only when given for hemoglobin level below 7 g/dL. In light of this, the administration of fluids is critical, and the decision of which fluids to administer is fundamental since the principal limiting factor is the time that these fluids remain in the intravascular system.

Transfusion practice during VA ECMO

Transfusion is more common in VA ECMO than in VV ECMO (8) because of the different pathophysiological setting. VA ECMO can unload the right ventricle and provide adequate oxygen to the end organs and system. It is likely that there is also an increased risk of bleeding due to arterial cannulations and more anticoagulation

requirements to avoid thrombosis in the heart and in low-flow territories (5,13,40,41). In fact, patients who require VA ECMO typically have a hemostatic imbalance at the time of cannulation, and starting extracorporeal support is only an additional indication for anticoagulation therapy (42). Moreover, thrombocytopenia is frequent due to underlying illness, and the extracorporeal circuit can worsen this condition, leading to activation of inflammatory pathways and hemolysis (43). Indeed, platelets can adhere to surface fibrinogen, leading to thrombocytopenia. There is now a novel ECMO circuit that features reduced platelet adhesion and minor pro-inflammatory properties (44). Finally, a difference should be considered for central and peripheral cannulation since peripheral cannulation requires mandatory care of the SvO_2 because the venous blood that enters a damaged lung can carry prevalently poorly oxygenated blood flow to the brain.

In the setting of moderate to severe hemorrhage, it is probably safer to withhold anticoagulation for VV ECMO than it is for VA ECMO, even if several studies have reported no life-threatening thromboembolic complications after withholding anticoagulation therapy for days (41,45). In VA ECMO patients, even exposure to systemic anticoagulation only at the time of weaning resulted in a reduced risk of bleeding and blood transfusion requirements without a significant increase in thromboembolic events.

There is heterogeneity among centers regarding hemoglobin trigger used to transfuse patients on VA ECMO. As shown in *Table 3*, some centers adopt a restrictive approach while others remain anchored to a liberal approach to transfusion. As regard the trigger for transfusion, some centers adopt hemoglobin values, others hematocrit, and others do not specify the trigger used to guide transfusion. The survival to discharge and PRBC requirements remain variable.

Practices to reduce RBC transfusion during ECMO support

Several strategies can be employed by healthcare practitioners to decrease the requirement for RBC transfusion during ECMO support. Initially, minimizing blood loss through the reduction or limitation of blood samplings can be beneficial. Secondly, decreasing the duration of ECMO support may contribute to this goal (62). Lastly, standardizing transfusion practices via local protocols can provide a consistent approach to minimizing transfusion necessities (63,64).

Transfusion practice aims to increase oxygen delivery, yet there are different strategies to reach this objective without transfusing patients.

Blood flow rate

The blood flow rate during ECMO is usually set at 2–4 L/min, depending on the patient's size, cardiac function, and oxygenation needs. A higher blood flow rate can help improve oxygenation and remove carbon dioxide, but it also increases the risk of bleeding and other complications. Monitoring and maintaining fluid balance is a crucial aspect of the management of patients on ECMO support. In fact, hypovolemia leads to a reduced blood flow rate and hypoperfusion. On the other hand, fluid overload can also reduce the blood flow rate, increasing systemic blood pressure. Furthermore, the hemodilution induced by a positive fluid balance leads to a higher and inefficient blood flow rate because it will not be associated with higher oxygen delivery.

Autotransfusion during decannulation

One investigation (65) revealed a significant reduction in the volume of RBCs transfused due to autotransfusion during decannulation. The authors identified additional advantages of autologous blood transfusion, such as a diminished immune response, a decreased risk of infectious complications, a shorter duration of ICU stay, and an improvement in pulmonary function. In another study (63), autotransfusion is a practice incorporated within the patient blood management protocol.

Perfusion markers

As stated above, practitioners are more likely to transfuse ECMO patients, in order to decrease the risk of cardiac ischemia and to counteract bleeding and hemodilution induced by circuit priming. Despite several studies suggesting that a restrictive transfusion strategy can be safe and effective, other authors have raised concerns about applying such an approach in ECMO population, highlighting the importance of carefully assessing each patient's individual risk factors and clinical situation when deciding on the appropriate transfusion strategy. In reality, the predefined threshold-based approach may be inappropriate in the setting of VA-ECMO due to differences in DO2 requirements between patients based on their etiology, disease severity, and ECMO modality. In addition, large variations in DO2 can be observed in the same patient and between ECMO settings. From this perspective, practitioners should transfuse patients not to reach an established Hb value but to match metabolic

Table 3 Observational studies on transfusion practice during VA ECMO support

Author/year (ref.)	Study type	Indication type (surgical/non-surgical/mixed)	Indications	N	ECMO days (mean ± SD)	Transfusion trigger (g/dL or HCt%)	PRBC/day (mean ± SD)	Survival to discharge (%)
Bakhtiary 2008, (46)	Retrospective	Non-surgical	Hantavirus cardiopulmonary syndrome	45	6.4±4.5	NS	2.55±2.03	28.9
Cahill 2018, (47)	Retrospective	Non-surgical	CS	30	7.4±8.2	8 g/dL	NS	37.7
Esper 2015, (48)	Retrospective	Non-surgical	CS post-AMI	18	3.3±2.2	NS	3.47±2.36	66.7
Fagnoul 2013, (49)	Prospective	Non-surgical	eCPR	24	1.6±2.1	7 g/dL	8.90±11.25	25
Formica 2010, (50)	Retrospective	Mixed	CS	42	7.9±5.3	30%	3.10±3.90	38.1
Hryniewicz 2016, (51)	Retrospective	Mixed	CS	37	4.7±2.3	NS	2.52±1.61	64.9
Lamarche 2011, (52)	Retrospective	Mixed	CS	32	2.2±2.0	NS	9.08±8.66	NS
Li 2015, (53)	Retrospective	Surgical	CS postcardiotomy	123	4.3±3.7	30%	4.49±2.88	34.1
Loforte 2014, (54)	Retrospective	Mixed	CS	228	10.8±9.2	28%	1.29±1.03	63.2
Marasco 2010, (55)	Retrospective	Surgical	CS post-HTx	39	6.8±2.6	8 g/dL	3.15±1.99	NS
Mikus 2013, (56)	Retrospective	Surgical	CS postcardiotomy	14	9.0±13.8	28%	6.00±0.84	42.9
Mohite 2015, (57)	Retrospective	Mixed	CS	59	8.9±5.1	NS	2.56±1.81	NS
Muehrcke 1996, (58)	Retrospective	Non-surgical	CS	23	2.4±1.5	NS	17.84±8.88	31.8
Opfermann 2016, (59)	Retrospective	Surgical	CS postcardiotomy	300	6.1±4.8	NS	0.74±0.79	51.7
Staudacher 2016, (60)	Retrospective	Non-surgical	CS post-AMI; eCPR	90	2.2±2.7	8 g/dL	0.79±1.51	24.4
Müller 2009, (61)	Retrospective	Surgical	CS	60	9.0±6.1	8 g/dL	1.00±1.06	45

VA ECMO, venoarterial extracorporeal membrane oxygenation; SD, standard deviation; HCt, hematocrit; PRBC, packed red blood cell; CS, cardiogenic shock; AMI, acute myocardial infarction; eCPR, extracorporeal cardiopulmonary bypass; HTx, heart transplantation; NS, not specified.

demands. Therefore, a more individualized strategy guided by a DO2 surrogate, central venous oxygen saturation ($ScvO_2$), may be more appropriate in this population. The $ScvO_2$ approach has recently been shown to be associated with reduced PRBCs in two randomized controlled trials in cardiac surgery patients (66,67). Furthermore, looking at the trend in $ScvO_2$ might provide useful information on changes in oxygen extraction during transfusion and could ameliorate patient blood management in ECMO population.

Pulsating ECMO

Recently, there has been increasing interest in pulsatile ECMO as an alternative to continuous VA ECMO. Pulsatile flow should ameliorate end-organ perfusion, especially for brain, kidney and coronary circulation (68). Furthermore, it is believed that pulsatile flow can help to maintain microcirculation and reduce inflammation and thrombosis (69). Moreover, pulsatile flow may be crucial in unloading the left ventricle in refractory cardiogenic shock. If confirmed by future research, pulsatile VA ECMO may guarantee more efficient oxygen delivery and left ventricle unloading compared to classic non-pulsatile VA ECMO, and therefore might lead to a decrease in the need for transfusion.

Hybrid configurations

Several subsets of patients on ECMO support can experience a change in their condition and physiologic demand. For this reason, ECMO configurations have evolved from "pure" veno-venous or veno-arterial ECMO to more complex hybrid configurations, with the use of additional cannulas to dynamically match physiological needs over time (70). For example, patients supported with VV ECMO can have inadequate drainage or perfusion, cardiovascular failure (frequently of the right heart), and drops in oxygen delivery despite adequate oxygen uptake. The addition of a third cannula in these patients

can be critical in restoring the perfusion deficit and the unloading of the right or both ventricles. In patients on VV ECMO, cardiac unloading can be achieved with additional mechanical support devices, such as an intra-aortic balloon pump, counterpulsation or short-term assist devices (71). Similarly, patients on VA ECMO can develop a differential oxygenation as cardiac native function begins to recover. In this condition, the upper body can be less oxygenated (Harlequin syndrome or North/South syndrome), and an extra inflow cannula introduced into the internal jugular vein (veno-venoarterial extracorporeal membrane oxygenation or V-VA ECMO) can provide oxygenated blood to the left ventricle, and thus the coronary and aortic arch vessels. In general, inserting an additional cannula for hybrid ECMO carries further risk of bleeding in patients with therapeutic anticoagulation. Balancing risks and benefits when considering whether to initiate an advanced ECMO configuration is critical in avoiding wasted efforts to spare blood transfusions. ECMO with two oxygenators in parallel can improve oxygen uptake. This is particularly indicated when patients are developing multi-organ failure despite conventional ECMO configurations. The use of a double oxygenator system provides a backup in case of a malfunction or failure of one oxygenator, increasing the reliability of the ECMO system. More interesting is the use of two oxygenators in parallel, which may decrease resistance to blood flow leading to a reduction in blood trauma and shear stress.

Conclusions

PRBC transfusion has a questionable cost-benefit ratio. The most widespread clinical practice considers only the hemoglobin values when deciding a patient's transfusion needs. However, a growing body of literature suggests combining the hemoglobin value with physiological parameters, such as oxygen extraction to obviate the need for PRBC and improve patient blood management. As an increase in oxygen extraction can counteract the decrease in oxygen carrying capacity only in cases of isovolemic anemia, it is crucial to optimize fluid balance and dynamically adjust ECMO blood flow. Moreover, advances in medical technologies and clinical expertise will likely make ECMO circuits increasingly efficient in matching a patient's metabolic demand and reducing PRBC transfusion requirements.

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