ScvO 2 changes after red-blood-cell transfusion for anaemia in cardiothoracic and vascular ICU patients: an observational study

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$ScvO_2$ changes after red-blood-cell transfusion for anaemia in cardiothoracic and vascular ICU patients: an observational study

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Background and Objectives Haemoglobin threshold for transfusion has been significantly decreased, but haemoglobin plasma concentration may not be sufficient to assess the need of red-blood-cell (RBC) transfusion. Central venous oxygen saturation ($ScvO_2$) is a clue of metabolic matching between O_2 transport and consumption, which could help to assess when transfusion is appropriate once anaemia has been diagnosed in ICU patients.

Materials and Methods Adult patients admitted consecutively to a cardiothoracic and vascular ICU were included in a prospective, observational and single-centre study over a 6-month period (September 2014 to February 2015), provided they were transfused with RBC. Patients with active bleeding or in unstable condition were excluded. Haemoglobin and $ScvO_2$ were collected through a central venous catheter before and after transfusion. In order to identify a $ScvO_2$ threshold, analysis of $ScvO_2$ changes after transfusion was performed.

Results Fifty-three patients received 100 RBC transfusions. Haemoglobin at the time of transfusion was 7·2 g/dl [6·8–7·7], while $ScvO_2$ was 66·9% [60–73]. A 5% increase in $ScvO_2$ after transfusion has the best specificity and positive predictive values, with a $ScvO_2$ threshold of 65%. After transfusion (RBC units, 2 [1-2]), $ScvO_2$ increased only in patients with $ScvO_2$ ≤65%, from 58% [53–62] to 69% [64–73] ($P < 0·001$).

Conclusion In anaemic patients, RBC transfusion induced a significant increase in $ScvO_2$, provided it was low before transfusion. A 65% cut-off value of $ScvO_2$ before transfusion showed good specificity and good positive predictive value for a 5% increase after transfusion.

Key words: anaemia, ICU, $ScvO_2$, transfusion.

Introduction

Anaemia occurs frequently during critical illness. A haemoglobin concentration (Hb) less than 12 g/dl is common in an ICU, even more likely after cardiac surgery [1–4].

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Optimal management of the anaemia of critical illness is controversial. Up to 50% of ICU patients receive red-blood-cell (RBC) transfusions [5, 6], out of which only 20% are to treat haemorrhage [1]. In cardiac surgery, the majority of the patients receive 3 or less RBC units [4]. However, the benefit–risk balance of a blood transfusion is a serious concern since several studies have shown that it may be associated with increased morbidity and mortality, even for few RBC units [7–9].

The decision to transfuse is currently referred to guidelines based on the Hb, and a threshold of 7–9 g/dl is

recommended [10, 11]. Nevertheless, several authors have criticized a highly restrictive transfusion strategy [12–14]. A recent study, which compared restrictive vs. liberal strategy in post-cardiac surgery patients (Hb <7·5 g/dl and <9 g/dl, respectively), showed no difference between the two strategies in morbidity, although there was an increase in 3-month mortality in the restrictive group [15].

Therefore, Hb level may not be sufficient to assess the need for transfusion.

As Hb is an oxygen carrier, the question is whether an increased Hb following transfusion matched the metabolic demand. A possible option is to measure mixed venous oxygen haemoglobin saturation (SvO_2), which reflects the balance between oxygen delivery and oxygen tissue consumption. To measure SvO_2, a pulmonary artery catheter is required, but central venous oxygen haemoglobin saturation ($ScvO_2$) requires only a blood sample collected from central venous line. $ScvO_2$ represents the oxygen Hb saturation of the superior vena cava territory, and therefore, it does not take into account the oxygen saturation of the inferior vena cava compartment and coronary sinus. Despite a lack of exact numerical equivalence, their variations are parallel with a satisfactory correlation [16, 17].

We proposed to study the effect of blood transfusion on $ScvO_2$ in anaemic patients admitted to a cardiovascular and thoracic ICU.

Material and methods

This is a prospective, observational single-centre study conducted over a 6-month period from September 2014 to February 2015, in a 14-bed cardiovascular and thoracic ICU at the Montpellier Academic Hospital, France. The study was submitted to the Montpellier University Hospital institutional review board, which, because of the observational nature of the study, waived the need for informed consent.

Patients

All adult patients admitted consecutively to the ICU were included, provided they had an indication for RBC transfusion (Hb <9 g/dl, based on European Society of Anaesthesiologists Guidelines [18]), and a central venous catheter located in the superior vena cava territory (subclavian vein or internal jugular vein). Central venous catheter position was verified by chest X-ray in the immediate postoperative period.

In order to evaluate anaemia in the absence of critical conditions, patients with the following conditions were excluded: acute bleeding requiring transfusion of more than 4 RBC units in 24 h or requiring a second operation for homeostasis (severe stage based on the criteria of the Universal Definition for Perioperative Bleeding [19]), patients who had major changes in respiratory therapy (change in mechanical ventilation mode or FiO_2 concentration >15%), or in hemodynamic treatment (fluid volume loading, introduction of catecholamine or a dose increase of more than 20%, or change in transient circulatory support settings), or change in sedation level between the two measurements of $ScvO_2$.

Transfusion

RBC transfusion was managed as routinely, according to national guidelines (Agence Française de Sécurité Sanitaire des Produits de Santé, AFSSAPS 2002).

The number of RBC units (NRBC) to be transfused depended on patient's estimated blood volume (VST), Hb concentration before transfusion (Hbi) and expected Hb concentration after transfusion (Hbd, i.e. 9 g/dl), and the Hb concentration of the RBC unit (QHbRBC) according roughly to the following formula:

$$N_{RBC} = (VST/100)(Hb_d - Hb_i)/QHb_{RBC}$$

Measurements

Besides patient characteristics, hemodynamic parameters, sedation (Richmond Agitation-Sedation Scale, RASS) and pain (behaviour pain score, BPS) scores, respiratory parameters, cardiac support (inotropes and/or assistance) and Hb level were recorded at the time the decision to transfuse was made. The number of RBC units and therapeutic changes between the two samples of $ScvO_2$ were also collected.

$ScvO_2$ was measured by cooxymetry with a point-of-care blood gas analyser located in the ICU (Instrumentation Laboratory, GEM 4000 Premier, USA) from blood samples taken in the superior vena cava through the central venous catheter, before and after RBC transfusion.

Statistical analysis

Quantitative variables are expressed as median and 25–75 interquartile [IQ], qualitative variables as a percentage. Statistical analysis was performed using the Mann–Whitney nonparametric model for quantitative variables and chi-squared test for qualitative variables.

The relationship between Hb and $ScvO_2$ was analysed by Spearman rank correlation coefficient.

To determine the best $ScvO_2$ value to predict an increase in $ScvO_2$ following transfusion, an analysis of receiver operating characteristics (ROC) curves was performed using four levels of $ScvO_2$ increase (5, 10, 15 and

20%). We anticipated choosing the $ScvO_2$ with the best positive predictive value, able to select patients who may benefit of a $ScvO_2$ increase after transfusion with the lowest rate of false positives.

The statistical analyses were performed with GRAPH PAD PRISM (version 5.0, 2008) and XLSTAT 7.5.2 (Addinsoft, Brooklyn, NY). Statistical significance was considered achieved with an alpha risk of <5% ($P < 0{\cdot}05$).

Results

Population studied

Fifty-three ICU patients had received transfusions.

Patients' medical history and admission pattern are reported in Table 1. Most patients were admitted following surgery (40, 76%) and others for medical issues including temporary circulatory extracorporeal assistance (8, 15%). Transfusion episode per patient was 1 [1, 2], and most patients (78%) had one or two transfusion episodes, which resulted in a total of 104 RBC transfusions.

Table 1 Patient characteristics

	Patient population (n = 53)
Age, years, median [IQ]	67 [57–73]
Male, *n* (%)	36 (68)
Medical history	
Diabetes, *n* (%)	15 (28)
Hypertension, *n* (%)	27 (51)
Coronary artery disease, *n* (%)	27 (51)
Chronic renal failure, *n* (%)	8 (15)
LVEF, %, median [IQ]	20 [15–40]
SAPS II, median [IQ]	52 [36–60]
Admission pattern	
Cardiac surgery, *n* (%)	25 (47)
CABG, *n* (%)	4 (7·5)
Valvular, *n* (%)	8 (17)
CABG & valvular, *n* (%)	2 (3·7)
Aortic dissection, *n* (%)	2 (3·7)
LVAD, *n* (%)	7 (13·2)
Other, *n* (%)	2 (3·7)
Major thoracic surgery, *n* (%)	3 (5·6)
Major vascular surgery, *n* (%)	12 (22·6)
Transient circulatory assistance	
ECLS or Impella, *n* (%)	5 (9·4)
VV ECMO, *n* (%)	3 (5·6)
Medical (cardiogenic shock), *n* (%)	5 (9·4)

[IQ], 25-75 interquartile; LVEF, left ventricular ejection fraction; SAPS II, Simplified Acute Physiology Score II; CABG, coronary artery bypass graft; LVAD, left ventricle assistance device; ECLS, veno-arterial extracorporeal life support; VV ECMO, veno-venous extracorporeal membrane oxygenator.

RBC Transfusions

From 104 RBC transfusions, three were excluded due to change in patient's condition during transfusion: one for respiratory parameters, one for sedation score, one for norepinephrine dose increase and one was not included because SvO_2, instead of $ScvO_2$, was measured from a pulmonary artery catheter. Finally, 100 RBC transfusions were included in the study; the pre-transfusion characteristics are reported in Table 2.

Sixty-two RBC transfusions had available data on the cardiac function assessment by echocardiography (Doppler transaortic time velocity integral) before transfusion (Table 2). Twenty-eight RBC transfusions were performed in patients on circulatory support.

Fifty transfusions (50%) were performed during mechanical ventilation, either in volume-controlled ventilation (76%) or in pressure support ventilation (24%).

Patients with assisted ventilation were sedated with a RASS score at −4[−4–3] and BPS at 3 [3]. Fifty RBC transfusions were given to patients who were spontaneously breathing either with non-invasive ventilation (n = 5) or during nasal oxygen administration (n = 45), including high flow oxygen (n = 14). Before transfusion, Hb was 7·2 g/dl [6·8–7·8] vs. 7·2 g/dl [6·8–7·8] ($P = 0{\cdot}85$), and ScvO2 was 66·7% [60–72] vs. 67·1% [61–79] ($P = 0{\cdot}94$) for spontaneously breathing and extubated patients vs. intubated patients with assisted ventilation, respectively. ScvO2 after transfusion was similar in both groups 72·7% [66–75] vs. 71·5% [66–77] ($P = 0{\cdot}94$) for spontaneously breathing and extubated patients vs. intubated patients with assisted ventilation, respectively.

Haemoglobin and $ScvO_2$ changes after transfusion

Anaemia was severe and was corrected appropriately by the transfusion protocol, with a median transfusion of 2 [1, 2] RBC units (Table 3). $ScvO_2$ increased significantly (Table 3) with a median delay between the two $ScvO_2$ measurements of 137 minutes [90–290].

There was no significant correlation between the Hb level and $ScvO_2$ before transfusion according to the Spearman analysis [$r = 0{\cdot}001$; (IC95: −0·2–0·2) $P = 0{\cdot}99$] (Fig. 1).

The best values of $ScvO_2$ to predict an increase of 5%, 10%, 15% and 20% after transfusion were 65%, 61·9%, 60% and 59%, respectively (Table 3).

The area under the curve of the ROC curves increased with the level of $ScvO_2$ change, mainly due to the increase in the sensitivity, reaching 100% at 20% $ScvO_2$ post-transfusion increase (Table 4). The $ScvO_2$ of 65%, which was associated with a 5% $ScvO_2$ increase after transfusion, had the best specificity and positive predictive value (Table 4) (Fig. 2).

Table 2 Clinical status before the RBC transfusion

	All (n = 100)	$ScvO_2 \leq 65\%$ (n = 42)	$ScvO_2 > 65\%$ (n = 58)	P^a
Delay form ICU admission, days, median [IQ]	4 [1–11]	3 [1–11]	4 [1–11]	0·66
AoTVI*, cm, median [IQ]	17 [14–20]	17 [13–21]	18 [15–20]	0·97
Norepinephrine, n (%)	64 (64)	31 (73·8)	33 (56·9)	0·12
Inotrope, n (%)	6 (6)	1 (2·3)	5 (8·6)	0·34
Lactate, mmol/l, median [IQ]	1·6 [1·1-2·2]	1·6 [1·1-2·3]	1·7 [1·1-2]	0·52
SOFA score, median [IQ]	7 [4–14]	6 [4–14]	7 [4–14]	0·47
Mechanical ventilation, n (%)	50 (50)	17 (40·5)	33 (56·9)	0·11
SaO_2, %, median [IQ]	100 [98-100]	100 [98-100]	100 [98-100]	0·47

[IQ], 25-75 interquartile;; AoTVI, Doppler transaortic velocity integral (* available in 62 cases); SOFA, Sequential Organ Dysfunction Score.
[a]P value between $ScvO_2 \leq 65\%$ vs. $ScvO_2 > 65\%$.

Table 3 Effects of RBC transfusion

	All (n = 100)	$ScvO_2 \leq 65\%$ (n = 42)	$ScvO_2 > 65\%$ (n = 58)	P^a
Before transfusion				
Hb, g/dl	7·2 [6·8–7·7]	7·2 [6·7–7·6]	7·2 [6·8–7·7]	0·61
Heart rate, bpm	89·5 [76–101]	93 [75–106]	86 [76–99]	0·27
MAP, mm Hg	74 [70–84]	75 [70–84]	74 [69–84]	0·75
$ScvO_2$, %	66·9 [60–73]	58·4 [53–62]	72 [68–78·9]	0·001
EO_2, %	32·4 [25·9–39·6]	40·2 [36·9–46·1]	26·2 [20·7–31·2]	0·001
Transfusion				
PRBC units	2 [1,2]	2 [1·7–2]	2 [1,2]	0·67
After transfusion				
Hb, g/dl	9·1 [8·5–9·8]*	9·1 [8·5–9·6]*	9 [8·6–9·6]*	0·93
Heart rate, bpm	90 [77–99]	88 [78–100]	90 [76–99]	0·76
MAP, mm Hg	80 [74–90]	80 [75–86]	80 [72–90]	0·89
$ScvO_2$, %	72 [66–77]*	69 [64–73]*	74 [69–79]	0·81
EO_2, %	28·1 [22·6–33·1]*	30·3 [26·6–36·1]*	24·4 [20·9–31·0]	0·001

Hb, hemoglobin level; MAP, mean arterial pressure; EO_2, O_2 extraction as $(SaO_2\text{-}ScvO_2)/SaO_2$ in %; PRBC, packed red blood cell.
Data are expressed as Median [25–75 Interquartile].
[a]P value between $ScvO_2 \leq 65\%$ vs. $ScvO_2 > 65\%$.
*$P < 0{\cdot}001$ vs. before transfusion.

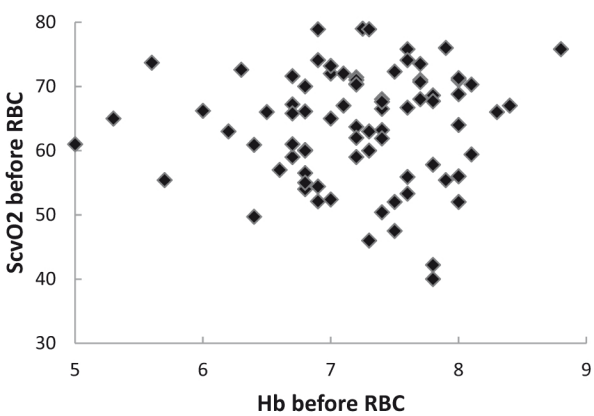

Fig. 1 Correlation between haemoglobin level (Hb) and $ScvO_2$ before transfusion. Haemoglobin level and $ScvO_2$ are not correlated according to Spearman analysis [r = 0·001; (IQ95: –0·2–0·2), P = 0·99].

Using this criterion to compare patients with or without $ScvO_2 \leq 65\%$, we observed that the pre-transfusion characteristics were similar between both groups (Table 2). ScvO2 increased significantly only in patients with $ScvO_2 \leq 65\%$, while Hb increase was similar in both groups (Table 3).

There were no significant differences between both groups in hemodynamic measurements (Table 3). The lower $ScvO_2$ in patients with $ScvO_2 \leq 65\%$ was associated with a higher EO_2 when compared to others (Table 3).

Discussion

This study shows that in patient, with severe anaemia (Hb at 7·2 g/dl) in a cardiovascular and thoracic ICU, $ScvO_2$ lower than 65% has a good positive predictive value

Table 4 $ScvO_2$ cutoff value to predict an increase after transfusion

$ScvO_2$ increase	$ScvO_2$ cutoff value%	Sensitivity% (IQ95%)	Specificity% (IQ95%)	PPV%	NPV%	AUC (IQ95%)
+5%	65	68 (54·1–79·2)	88 (75·7–94·7)	85	73·3	0·82 (0·74–0·90)
+10%	61·9	82·6 (62·1–93·5)	84·4 (74·5–91)	61·3	94·2	0·88 (0·79–0·94)
+15%	60	82·2 (53·8–96·2)	84·1 (74·9–90·4)	41·7	97·4	0·87 (0·76–0·97)
+20%	59	100 (45–100)	82·3 (73·3–88·7)	19	100	0·92 (0·86–0·97)

PPV, Predictive positive value; NPV, Negative predictive value; AUC, Area Under the ROC Curve.

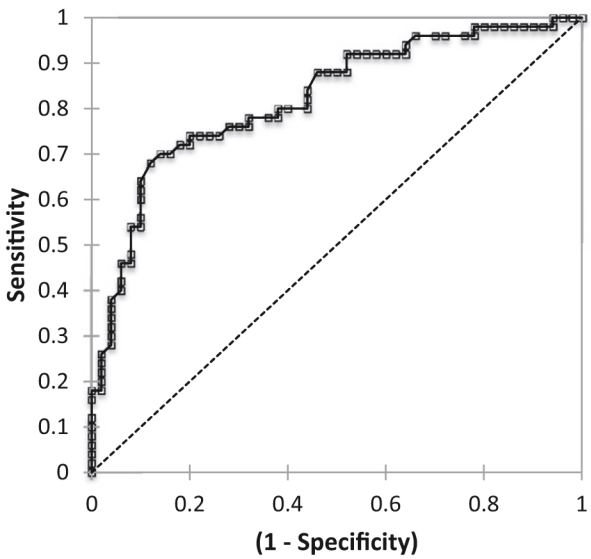

Fig. 2 Receiver operating characteristics ROC curve for 65% $ScvO_2$ cut-off value. Receiver operating characteristics curve for a $ScvO_2$ of 65%. To detect a 5% increase in $ScvO_2$ after transfusion of packed red blood cells, a $ScvO_2$ threshold of 65% has a sensitivity of 68% [54·1–79·2] and a specificity of 88% [75·7–94·7]. Area under the curve was 0·82 [0·74–0·90] ($P < 0·001$).

(85%) to predict a $ScvO_2$ increase of 5% after RBC transfusion.

$ScvO_2$ is a parameter that reflects the balance between oxygen transport (DO_2) and tissue oxygen consumption. $ScvO_2$ varies then with oxygen content of arterial blood (CaO_2) that depends mainly on SaO_2 and Hb levels, cardiac output (CO) and body oxygen consumption (VO_2). When SaO_2 and VO_2 are kept constant, as it is likely in this study, $ScvO_2$ could vary only with Hb or CO. Our data suggest that anaemic patients with $ScvO_2$ ≤65% depend on O_2 extraction for adapting DO_2 [20]. Interestingly, there was no significant difference in hemodynamic characteristics when available and treatment, including mechanical circulatory support between patients, whatever the pre-transfusion $ScvO_2$ level (Table 2). Most patients had limited cardiovascular function (low LVEF), a condition where anaemia tolerance can be more sensitive than in patients with normal cardiac function who can adapt DO2 by increasing CO. However, LVEF was assessed preoperatively, and Ao TVI, which was measured in ICU before transfusion, was not low, which suggests that the hemodynamic stability was not too compromised at the time of transfusion. From the data of the study, we can speculate that the increase in ScvO2 when it is below 65% may result from CaO2 increase, CO increase or both. Whatever the underlying mechanism behind the increase in ScvO2, transfusion is then the appropriate treatment for the anaemia because increasing CO only by fluid loading, like crystalloids without RBC transfusion, would have resulted in anaemia worsening. Conversely, the absence of increase in ScvO2 when ScvO2 is above 65% may result from a CO adaptation. Therefore, ScvO2 could help to identify anaemic patients who may not need transfusion, beyond 'macro-hemodynamic' parameters and to limit irrelevant transfusion.

The rationale for RBC transfusion is to increase the amount of oxygen distribution, assuming that tissue oxygen demand will be better covered, avoiding a gradual switch from aerobic metabolism to anaerobic conditions. Maintaining tissue oxygenation is considered as an important prognostic factor in terms of morbidity and mortality [17, 21]. However, Marik *et al.* found no reduction in mortality and morbidity when they attempted to raise $ScvO_2$ above the normal range in ICU patients [22]. Therefore, the best option for an effective transfusion seems to get an Hb high enough to avoid low $ScvO_2$.

The question of the lowest $ScvO_2$ level acceptable to ensure adequate matching between DO_2 and VO_2 has already been addressed although most studies were aimed at determining the optimal $ScvO_2$ threshold to reduce the risk of complications, besides the context of anaemia or transfusion [23–25].

Fewer studies have addressed the issue of $ScvO_2$ in anaemic conditions. In patients with anaemia who underwent general surgery, Vallet *et al.* found a $ScvO_2$ value of 69·5% for predicting a 5% increase after erythrocyte transfusion [26]. We also observed that increasing the $ScvO_2$ percentage change to higher values (from 5 to

20%) improves the sensitivity of the $ScvO_2$ cut-off value, but at the expense of specificity, down to 59%. The lower the $ScvO_2$ before transfusion, the higher the increase in $ScvO_2$ after transfusion, which follows the physiology of VO_2/DO_2 dependence and may not be clinically relevant [20]. Therefore, choosing the $ScvO_2$ with the best positive predictive value and specificity (65%) seems the most appropriate strategy [27, 28]. With a 65% $ScvO_2$ cut-off value, we were able to identify a fraction of anaemic situation (42%), out of which more than 80% had a significant $ScvO_2$ increase after blood transfusion. Our results suggest that RBC transfusion could have been possibly avoided in almost 60% anaemic patients with high $ScvO_2$. For these patients, alternative treatments of anaemia, like intravenous iron supplementation or erythropoietin, could have been preferred to RBC transfusion. Indeed, assuming that high $ScvO_2$ reflected normal O_2 extraction, there was no need to correct anaemia urgently [29]. However, reducing Hb transfusion threshold with $ScvO_2$ adjustment to calibrate restrictive transfusion strategy requires further studies; the impact of a $ScvO_2$-directed restrictive strategy is already under investigation (NCT 02761564).

This study has several limits. First, it is a single-centre, observational study.

Second, although we attempted to avoid possible changes in clinical conditions, we cannot completely exclude that ScvO2 determinants besides Hb (CaO2, CO, EaO2) have changed during the observational period. However, no significant difference on hemodynamics between the two groups was noticeable before or after transfusion (Table 3).

Finally, the impact of the volume load related to the transfusion on the increase in cardiac performance is unknown as we did not measure CO in each patient. However, the absence of significant difference in hemodynamic status before and after transfusion, and similar volume of RBC transfusion between lower vs. higher $ScvO_2$ make this hypothesis unlikely. Furthermore, if $ScvO_2$ value during anaemia is useful to guide transfusion for correction of anaemia per se, it would help even further to correct 'anaemia with hypovolemia' eventually.

In conclusion

In this observational study in anaemic cardiovascular and thoracic ICU patients, in the absence of acute haemorrhage, RBC transfusion does not improve $ScvO_2$ in patients with initial $ScvO_2 > 65\%$. Conversely, the change was significant when $ScvO_2$ was below 65% before transfusion. $ScvO2 \leq 65\%$ could be a good threshold for tailoring RBC transfusion to metabolic need in anaemic patient. Further studies are required to assess if this strategy may affect long-term prognosis and transfusion strategy.

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