ECRONICON OPEN ACCESS

EC EMERGENCY MEDICINE AND CRITICAL CARE
Research Article

Effect of Erythrocyte Transfusion on Hemodynamic and Oxygenation Parameters in ICU Patients

Ahlem Trifi*, Asma Mehdi, Yosr Touil, Foued Daly, Cyrine Abdennebi, Sami Abdellatif and Salah Ben Lakhal

Medical Intensive Care Unit, University Hospital Center La Rabta and Faculty of Medicine, University Tunis, El Manar, Tunis, Tunisia

***Corresponding Author:** Ahlem Trifi, Medical Intensive Care Unit, University Hospital Center La Rabta and Faculty of Medicine, University Tunis, El Manar, Tunis, Tunisia.

Received: June 07, 2021; **Published:** June 30, 2021

Abstract

Objective: To investigate the effects of erythrocyte transfusion (ET) on systemic hemodynamic and oxygenation variables in ICU patients with non-hemorrhagic anemia.

Methods: A cross-sectional study with a comparative approach on paired series (before versus after ET) conducted in the medical intensive care unit (ICU) of the Rabta University Hospital Center, Tunis-Tunisia during a period of 1 year (July 2019 - July 2020). Were included, patients receiving ET for non-hemorrhagic anemia. Hemodynamic and oxygenation parameters were obtained using cardiac Ultrasound-Doppler coupled with arterial and central venous gases. All parameters were taken just before ET and compared with those taken 2 hours after ET. Secondly, the analysis was adjusted according to the presence or not of septic shock.

Results: 50 ET were studied in 36 patients. The transfusion of 1 RBC induced: a significant increase in Hb (from 6,8 to 7,9 g/dl, $p < 10^{-3}$), in CaO_2 (from 9.2 to 10.5 ml/dl, $p < 10^{-3}$) and in $ScVO_2$ (from 73.5% to 78%, p = 0.002) with a significant decrease in CO (from 5.77 to 4.7 l/mn, p = 0.009). The increase in Hb and CaO_2 did not increase O_2 delivery (DO_2: from 526 to 514 ml/mn, p = 0.68) that it was related to the decrease in CO. Also, lactates level not changed. In patients with septic shock, it was revealed a significant decrease in CO and DO_2 without change in $ScVO_2$.

Conclusion: Despite the raise in Hb and CaO_2 after ET, DO_2 did not increase due to the decrease in CO resulting from the blood hyperviscosity. In patients with septic shock, DO_2 even decreased.

Keywords: *Red Blood Cells; Transfusion; Cardiac Output; Haematosis; Intensive Care*

Abbreviations

CaO_2: Arterial Oxygen Content; CBC: Cell Blood Count; CI: Cardiac Index; CI: Collapsibility Index; CO: Cardiac Output; DO_2: Oxygen Delivery; ET: Erythrocyte Transfusion; Hb: Hemoglobin; Ht: Hematocrit; ICU: Intensive Care Unit; IVC: Inferior Vena Cava; LVEF: Left Ventricular Ejection Fraction; RBC: Red Blood Cells; ScVO2: Central Venous Oxygen Saturation; SPAP: Systolic Pulmonary Artery Pressure; TBQ: Transfused Blood Quantity; TBV: Total Blood Volume; TTE: Trans-Thoracic Echocardiography; WHO: World Health Organization

Introduction

Anemia is a common event in intensive care unit (ICU) patients. The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) level less than 13 g/dl in men and 12 g/dl in women [1]. Upon admission in ICU, anemia affects two-thirds of patients, with an average Hb level at admission of 11.0 g/dl [2,3]. During the ICU stay, repeated blood spoliations (blood samples, invasive procedures, sur-

gery, etc), hemodilution and inflammation lead to a reduction in the Hb level [4,5]. ICU's anemia may increase the risk of failed weaning, the risk of myocardial infarction (due to an imbalance in oxygen supply and demand) and the risk of death [6]. The major concern with ICU's anemia is to improve hemoglobin levels by transfusions of concentrated red blood cells (RBCs) in order to increase the oxygen delivery (DO_2). However, several studies not showed an improvement in oxygen uptake post-RBC transfusion. In addition, the risks incurred by transfusion, even not very common, are potentially severe to justify a prior evaluation of the benefit/risk ratio.

Several clinical trials in ICU patients failed to demonstrate superiority in mortality of the liberal transfusion strategy compared to the restrictive transfusion strategy [7,8]. Hence, the ICU transfusion rate is regressing over the years as reported by the large reanalysis of databases from two observational studies conducted 13 years apart [9]. The investigators revealed a regression of the ICU transfusion rate by 13% and a similar ICU mortality despite the more severity illness in patients of the second period [9].

Optimal transfusion practice, in ICU patients, remains a matter of ongoing debate mainly about the benefits, risks and indications. In this perspective, we aimed to investigate the effects of erythrocyte transfusion (ET) in ICU patients (excluding acute hemorrhage) by comparing the hemodynamic/oxygenation and hematological variables before versus after ET.

Methods

Study design and ethical status: It was a cross-sectional, comparative study on paired series (before versus after ET) over 1 year (July 2019 - July 2020) carried out in the medical ICU of the University Hospital Center of la Rabta. Our medical staff adopts the conservative strategy of ET outside of an acute hemorrhage or intolerance signs of anemia and acute coronary syndrome. Thus, an Hb level less than 7 g/dl indicated ET. The study was approved by the local ethics committee. Due to the lack of interventional character, informed consent was not required and patients or their legal representative were informed. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Study population: Analyzed were the ET's cases, thus a patient could be included more than once. For ethical reasons and in order to avoid evaluation bias, we opted for that a patient cannot be included more than 3 times and the required interval between one transfusion and another must exceeded 72 hours. Adult (18 years of age or older) ICU inpatients monitored using trans thoracic cardiac ultrasound who received RBC concentrates for treatment of inflammatory anemia not related to acute hemorrhage were eligible for study inclusion. The indication for ET was made independently from the study by the ICU physicians in charge and it was motivated when hemoglobin level dropped below 7 g/dl.

Exclusion criteria were: acute hemorrhage, poorly tolerated anemia with clinical signs (tachycardia, polypnea, chest pain or neurological repercussions), transfusion accident, death or discharge within 24 hours of the ET and poor echogenicity.

Study protocol and used devices: Baseline Hb, trans-thoracic echocardiography (TTE)-Doppler and oxygenation measurements were taken just before and 2 hours after ET. The average duration of transfusion was in the order of 2 hours. For the first 15 minutes, the RBC pellet was transfused slowly at 5 ml/min, and then the perfusion flow was adapted to the clinical tolerance. A cell blood count (CBC) was taken 24 hours after the transfusion. Checking of Rhesus/ABO compatibility on hematology laboratory and bedside was the rule.

The TTE-Doppler evaluation was performed by two independent operators trained in ultrasound explorations in intensive care. We used an ultrasound device (Model: Aloka-ARIETTA V60, manufactured in 2014, company: Hitachi, Ltd, Chiyoda, Tokyo, Japan), equipped with a 5 MHz Convex piezoelectric probe and a pulsed, continuous, color and tissue Doppler imaging program.

Oxygenation evaluation was obtained by taking an arterial blood gas (ABG) concomitant with venous blood gas (VBG) via a central venous catheter. ABG was required for the calculation of arterial oxygen content (CaO_2) and O_2 delivery (DO_2). Venous gas was required

to determine the central venous oxygen saturation ($ScVO_2$). The device used for the measurement of blood gases was: Instrumentation laboratory GEM Premier 3500 (Werfen France). Note that the GEM Premier 3500 system measures blood gases (pH, pO_2, pCO_2), electrolytes (Na^+, K^+, Ca^{++}), metabolites (Glucose, Lactate), and Hematocrit. Oxygen saturation and bicarbonates are calculated from the aforementioned measurements.

Studied parameters: The following variables were taken and compared by pairing before/after RBC transfusion:

- Hemodynamic variables included: Cardiac output (CO)/cardiac index (CI), left ventricular ejection fraction (LVEF), E/A, E/E', Collapsibility index (CI in spontaneous ventilation) or distensibility index (DI in mechanical ventilation) of the inferior vena cava (IVC) and Systolic pulmonary artery pressure (SPAP).

- Hematologic and oxygenation variables: Were collected, Hb level (g/dl) and RBC count (10^6/ml), all parameters of ABG (pO_2, pCO_2, SaO_2, HCO_3^-, lactates), $ScVO_2$ from VBG, CaO_2 was calculated as $CaO_2 = (1.39 \times Hb \times SaO_2) + (0.003 \times PaO_2)$ (ml/dl of blood) and DO_2 calculated as $DO_2 = CaO_2 \times CO \times 10$ (ml/mn).

Collected data and statistical analysis: in addition to the specific study parameters detailed above, demographic, clinical and paraclinical data were collected and saved on an electronic database. Since the response to ET is closely dependent on preload, vasogenic status (which is susceptible to immune-inflammatory reactions) and underlying cardiac function, a complement analysis was made on subgroups according to the presence or not of septic shock.

IBM SPSS Statistics 20 (SPSS inc., Chicago, IL, USA) was used for all statistical analyzes. Quantitative variables were expressed as mean ± SD (for continuous and normally distributed ones) and as median [25%-75% percentile (interquartile range: IQR)] for continuous non-normally distributed ones. Qualitative variables were expressed as percentages.

The comparison of studied variables used the comparison tests of paired samples: T test for the Gaussian data and nonparametric Wilcoxon test for the non Gaussian data. A p-value < 0.05 was retained for statistical significance.

Results

Patient's flow: 50 acts of RBC transfusion in 36 patients were studied: 4 patients had 3 transfusions and 6 patients had 2 transfusions. No major transfusion incident was observed (Figure 1).

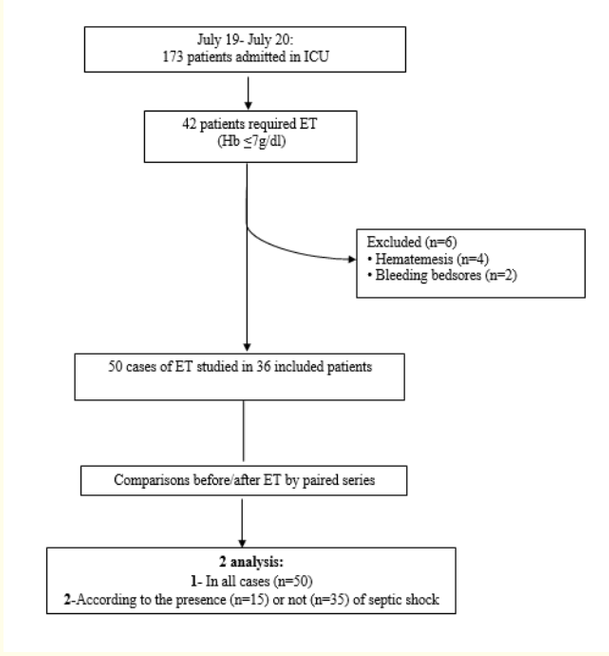

Figure 1: *Study flowchart.*
ET: Erythrocyte Transfusion; Hb: Hemoglobin.

Baseline clinical characteristics: The average age was 55 years and gender-ratio = 0,8. Diabetes and hypertension were the major co morbidities. A history of blood disease was noted in 5 patients. At baseline, the patients have a stable status (hemodynamic and ventilation). Fifteen (30%) patients were in septic shock and their hemodynamic stability was sustained using vasopressors.

Baseline hematologic data: The rhesus positive A blood group was the predominant (20/36) followed by the O positive group (7/36). The median Hb at admission was 9.3 g/dl [8 - 11.6] and at inclusion was 6.5 ± 0.6 g/dl. The mean Hb loss was 2.3 ± 1.4 g/dl. All baseline characteristics are displayed in table 1.

	Studied patients (n = 36)
Demographic data:	
• Sex-ratio (M/F)	0,8 (16/20)
• Age (years), mean ± SD [min-max]	55 ± 15 [23 - 88]
• BMI (kg/m^2), mean ± SD [min-max]	28 ± 6 [16 - 44]
Origin, n (%):	
• Emergency department	19 (53)
• Other structure	17 (47)
Reasons for ICU admission, n (%):	
• Respiratory	24 (67)
• Neurological	5 (14)
• Metabolic	5 (14)
• Hemodynamic	2 (5)
Co morbidities, n (%):	
• Diabetes	14 (39%)
• Hypertension	12 (34%)
• Chronic respiratory failure	6 (17%)
• Coronary artery disease	4 (11%)
• Renal failure	3 (8%)
• Hemopathy	5 (14%)
• Stroke	1 (3%)
Admission severity score: med [IQR]	
• SAPS II	41 [29 - 46]
• APACHEII	19,5 [15 - 25]
• SOFA	5,5 [3,2 - 7]
• CHARLSON	1 [0 - 2]
	Studied cases (n = 50)
Hemodynamic status at inclusion: med [IQR]	
• MAP (mm Hg)	83 [75 - 97]
• HR (beats/mn)	99 [85 - 120]
• Septic shock, n (%)	15 (30)

Respiratory status at inclusion: med [IQR]	
• FiO_2 (%)	0.4 [0.3 - 0.5]
• PEEP (cm H_2O)	6 [0 - 8]
• SpO_2 (%)	98 [96 - 100]
• P/F ratio	284 [199 - 374]
Hb level at admission, g/dl (Med [IQR])	9,3 [8 - 11,6]
Hb level at inclusion, g/dl:	
• Med [IQR]	6,8 [6,3 - 7]
• Hb range, g/dl (n):	
• 4-5	3
• 5-6	3
• 6-7	44
Hb Drop degree, g/dl	
Mean ± SD [min-max]	2,3 ± 1,4 [0,2 - 5,3]

Table 1: *Baseline characteristics.*

BMI: Body Mass Index, ICU: Intensive Care Unit, SAPS: Simplified Acute Physiology Score, Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, MAP: Mean Arterial Pressure, HR: Heart Rate, FiO_2: Inhaled Fraction Of Oxygen, PEEP: Positive End Expiratory Pressure, SpO_2: Pulsed Saturation.

Effect of erythrocyte transfusion:

- **On hematologic parameters:** Hb and RBC count increased considerably after ET.
- **On hemodynamic parameters:** the ultrasound measurements showed a significant decrease in CO/CI after ET estimated at 1 liter/mn for CO and at 0.53 l/mn /m^2 for CI (5.77 vs 4.7 l/mn, p = 0.009 and 3.58 vs 3.05, p = 0.002 respectively). No effect was found on the LV filling pressures or on the IVC variability.
- **On oxygenation parameters:** $ScVO_2$ and CaO_2 significantly increased from 73.5% to 78%, p = 0.002 and from 9.2 to 10.5 ml/dl, $p < 10^{-3}$ respectively. No change was demonstrated in DO_2. Similarly, lactate levels did not change.

Table 2 showed all the comparisons results.

	Before ET (n = 50)	After ET (n = 50)	p
Hemodynamic parameters			
SBP (mm Hg)	120 [110-140]	124 [108-137]	0,19
DBP (mm Hg)	66 [60-70]	67 [60-79]	0,16
MAP (mm Hg)	83 [75-97]	83,5 [74-100]	0,23
HR (bpm)	99 [85-120]	94 [80-120]	0,12
CVP (mm Hg)	5,7 [5-9]	6 [5-7,7]	0,81
LVOT VTI	22,3 [16,9-25,6]	19 [16,3-25,5]	0,14
CO (L/mn)	5,77 [4,3-7,01]	4,7 [3,67-6,71]	0,009
CI (L/mn/m^2)	3,58 [2,44-4,7]	3,05 [2,24-4]	0,002
E/A	1,12 [0,87-1,49]	1,04 [0,81-1,44]	0,79
E/E'	8 [5,06-10,8]	7,7 [5,5-11,7]	0,54
CI-IVC (%)	12,5 [5,7-29]	10 [5-20,7]	0,07
SPAP (mm Hg)	31 [25-40]	31,3 [25-41]	0,82

LVEF (%)	54 ± 13		
Oxygen metabolism parameters			
ABG values:			
• pH	7,36 [7,27-7,50]	7,34 [7,25-7,48]	0,9
• PO_2 (mm Hg)	107 [86-128,5]	107 [86,7-135]	0,46
• P/F ratio	284 [199-374]	300 [175-389]	0,34
• SaO_2 (%)	97 [96-98]	97,5 [95-98]	0,84
• $PaCO_2$(mm Hg)	48 [30-54]	49 [28-60]	1
• HCO_3- (mmol/l)	28 [16-36]	26,5 [16-38]	0.72
• Lactate (mmol/l)	2,2 [1,6-3,8]	1,9 [1,2-3,4]	0,13
VBG values:			
• pH	7,33 [7,22-7,49]	7,32 [7,20-7,51]	0,78
• PO_2 (mm Hg)	46 [30-55]	41,6 [36,7-45]	0,55
• PCO_2(mm Hg)	59 [44-68]	58 [45,6-66,8]	0,9
• HCO_3- (mmol/l)	27,4 [16,3-36]	27 [17,7-38]	0,77
• $ScVO_2$ (%)	73,5 [68,7-80]	78 [71,7-83]	0,002
Calculated values:			
• CaO_2 (ml/dl)	9,2 [8,6-9,6]	10,5 [9,5-11,3]	$< 10^{-3}$
• DO_2 (ml/mn)	526,4 [395,6-670,2]	514,5 [384-675,7]	0,68
Hematologic parameters			
Hb (g/dl)	6,8 [6,3-7]	7,9 [7,1-8,4]	$< 10^{-3}$
RBC count (10^6/ml)	2,49 [2,25-2,69]	2,87 [2,48-3,24]	$< 10^{-3}$

Table 2: *Comparison before versus after erythrocyte transfusion.*

E/E ': Early Diastolic Velocity Peak (E) divided by the maximum mitral ring velocity at the start of diastole (E'), CI-IVC: Collapsibility Index of Inferior Vena Cava, SPAP: Systolic Pulmonary Artery Pressure, LVEF: Left Ventricular Ejection Fraction, ABG: Arterial Blood Gases, VBG: Venous Blood Gases, SpO_2: Pulsed O_2 Saturation, PO_2: Arterial Oxygen Pressure, SaO_2: Arterial O_2 Saturation, $ScVO_2$: Central Venous O_2 Saturation, CaO_2: Arterial Oxygen Content, DO_2: Oxygen Delivery, Hb: Hemoglobin, RBC: Red Blood Cells.

Similar results were showed when the analysis was made only in the 36 patients (i.e. repeated measurements in the same patients were eliminated): Hb, $ScVO_2$ and CaO_2 increased significantly, CO decreased and DO_2 not changed (Table 3).

	Studied patients (n=36)		
	Before ET	**After ET**	**p**
CO (L/mn)	6,25 [4,39-7,22]	4,79 [3,64-6,93]	0,006
CI (L/mn/m^2)	3,93 [2,84-4,96]	3,08 [2,27-4,18]	0,003
$ScVO_2$ (%)	71,5 [67-80]	78,5 [70,25-84]	0,002
CaO_2 (ml/dl)	9,24 [8,66-9,55]	10,55 [9,55-11,4]	$<10^{-3}$
DO_2 (ml/mn)	572,25 [395-677]	518,5 [350-701]	0,98
Hb (g/dl)	6,85 [6,42-7,07]	7,9 [7-8,5]	$<10^{-3}$

Table 3: *Analysis excluding repeated measurements in the same patients.*
ET: Erythrocyte Transfusion, CO: Cardiac Output, CI: Cardiac Index, $ScVO_2$: Central Venous O_2 Saturation, CaO_2: Arterial Oxygen Content, DO_2: Oxygen Delivery, Hb: Hemoglobin.

Analysis according to the presence of septic shock: For patients in whom septic shock was diagnosed (n = 15): the effect of ET was similar to that previously found, in terms of CO/CI (which decreased), Hb and CaO_2 and (which increased). What differed from all previous results was the significant decrease in DO_2 (606 vs 545 ml/mn, p = 0.041). In addition, no effect was showed concerning $ScVO_2$. Lactates level tended to decrease following ET (from 4,4 to 3,7 mmol/l, p = 0,08). For patients without septic shock: CO/CI were unchanged, Hb, $ScVO_2$ and CaO_2 increased and a non-significant increase in DO_2 was noted (Table 4).

	Patients with septic shock (n = 15)			Patients without septic shock (n = 35)		
	Before ET	**After ET**	**p**	**Before ET**	**After ET**	**p**
CO (L/mn)	6,77 [5,84-8,3]	4,93 [3,69-6,99]	0,004	5,4 [3,49-6,85]	4,7 [3,6-6,7]	0,5
CI (L/mn/m^2)	4,36 [3,5-5,1]	3,08 [2,26-4,3]	0,003	3 [2,1-4,2]	2,9 [2,2-4]	0,15
$ScVO_2$ (%)	75 [70-82]	75 [70-83]	0,9	72 [67-80]	80 [72-84]	$< 10^{-3}$
CaO_2 (ml/dl)	9,35 [8,54-9,66]	10,55 [9,6-11,2]	0,011	9,2 [8,7-9,7]	10,5 [9,4-11,4]	$< 10^{-3}$
DO_2 (ml/mn)	606,3 [476-861]	545,7 [358-666]	0,041	468 [328-618]	507 [392-681]	0,064
Lactate (mmol/l)	4,4 [2,7-6,8]	3,7 [2-5,6]	0,08	1,6 [0,8-3]	1,3 [0,9-,2,8]	0,66
Hb (g/dl)	6,9 [6,3-7]	8 [7,2-8,4]	0,001	6,8 [6,4-7,1]	7,9 [7-8,6]	$< 10^{-3}$
Hematocrite (%)	21 [20,5-22,8]	25,5 [21,7-26]	0,005	21,1 [19,3-22,5]	24 [22,4-26,6]	$< 10^{-3}$
RBC count (10^6/ml)	2,5 [2,16-2,63]	2,84[2,5-3,11]	0,003	2,49 [2,27-2,81]	2,9 [2,48-3,4]	$< 10^{-3}$

Table 4: *Results according to the presence of septic shock.*
ET: Erythrocyte Transfusion, CO: Cardiac Output, CI: Cardiac Index, $ScVO_2$: Central Venous O_2 Saturation, CaO_2: Arterial Oxygen Content, DO_2: Oxygen Delivery, Hb: Hemoglobin, RBC: Red Blood Cells.

Discussion

Herein, we assessed the effects of RBC transfusion on advanced hemodynamic and oxygenation parameters obtained using TTE-Doppler and arterial with central venous gas in ICU patients. Following the transfusion of 1 unit of RBC concentrate, we noted a significant decrease in CO/CI and a significant increase in Hb, $ScVO_2$ and $CaO_2.DO_2$ and lactates were unchanged. Similar results were showed when the analysis excluded the repeated measurements in the same patients. In patients with septic shock: DO_2 decreased, $ScVO_2$ not changed and lactates tended to decrease.

In ICU patients, the main goal of RBC transfusion is to elevate oxygen delivery to the various tissues [10-12]. Yet, the threshold to indicate RBC transfusion is controversial. Between a conservative strategy with a threshold of 7 g/dl and a liberal strategy with a threshold of 10g/dl, opinions differ. In a systematic review including 31 randomized controlled studies with 9813 patients, there was no significant difference between these two strategies on the risk of death, morbidity and occurrence of heart attack [13].

A committee of 16 experts from four learned societies [SFAR (société française d'anesthesie reanimation), SRLF (société de reanimation de langue française), SFTS (Société Française de TransfusionSanguine) and SFVTT (Société française de vigilance et thérapeutique *transfusionnelle*) opt for the restrictive strategy (Hb threshold at 7.0 g/dL) in critical care patients in general, including septic patients, in order to reduce the need of transfusion without increasing morbidity and mortality [12].

Regarding the transfusion threshold in critical patients with chronic cardiovascular pathologies, the data are of low evidence levels. In our unit, we opt for the conservative strategy outside of head trauma or coronary patients where the thresholds are respectively 8 and 10 g/dl.

Effect of RBC transfusion on Hb and hemodynamic: The significant increase in hemoglobin and other hematological parameters that we noted agrees with the majority of reported data in literature [14-19].

On the other hand, we demonstrated a significant decrease in cardiac output that could be explained by the hyperviscosity of the blood (both Hb and RBC count increased significantly) and the lifting of the adrenergic response. In fact, anemia in normovolemic patients (excluding hemorrhagic context) is responsible for an increase in CO linked to two mechanisms: the decrease in blood viscosity and the adrenergic response responsible for a positive chronotropic and inotropic effect. Conversely, blood transfusion leads to an increase in hematocrit and therefore in blood viscosity and a lifting of the adrenergic response. This is how CO often decreases in isovolemic-patients. This significant drop in CO explains the decrease in oxygen delivery to peripheral tissues, rendering "abusive" transfusions unnecessary.

B Saugel., *et al*. [14] evaluated the effect of transfusing 2 RBCs for non-hemorrhagic anemia in 35 patients using the trans-pulmonary thermodilution technique (PiCCO) and concluded to similar results to ours. Indeed, the authors showed a significant decrease in CI (4.82 vs. 4.45, p = 0.004), and a non-significant drop in GEDVI (Global End Diastolic Volume Index). In our study, we used the E/E 'ratio as a preload-dependence marker which did not change before/after the RBC transfusion similarly to the preload parameter used by Sauget., *et al*. In addition, B Saugel., *et al*. revealed a significant drop in heart rate [14]. Thus, the significant decrease in CO was explained by the equally significant decrease in HR. This last data was not found in our study (99 vs 94 bpm, p = 0.12). As for the preload dependence parameters, the non-significant decrease was partly explained by the inclusion of isovolemic patient's (hemorrhage excluded) or who had a previous volume expansion.

Generally, the rationale for using ET to increase Hb concentration is to relieve cardiac work and, in severe cases, to correct the mismatch between O_2 delivery and O_2consumption [20]. However, the underlying cardiac preload and function may influence the responses

to ET. For example, in our patients' with septic shock requiring vasopressors, we noted a significant drop in O_2 delivery. That could be explained by a significant drop in cardiac output following ET, worsened by myocardial involvement linked to sepsis [21].

From another point of view, the decrease in CO following ET may be a good thing [22]. In fact, the main beneficial effect of transfusions may be to relieve the heart from the need to pump more. We can assimilate this effect by that of beta beta-blocking agents. After all, the primary indication for blood transfusion may be to support the heart. In this same direction, the reduction in heart rate in our series (99 to 94 bpm) although statistically not significant, it may be clinically valuable.

On the microcirculatory scale, the dysfunction of mitochondrial oxidative metabolism and the presence of arterio-venous shunt are also of the causes of impaired DO_2 [21]. Yet, our results as well as others should be interpreted with caution considering the small size. The great meta-analysis of Cavalcante Dos Santos E., *et al*. [20] (33 studies including 31 in prospective design and 14 of which were in septic patients) revealed a different results. Unlike our results, the authors not found a decrease in CO or HR following transfusion and have related that to a possible compensation by an increase in venous return due to a blood volume effect at least in some patients [20]. By comparing that to our data, this result was found in non-septic patients who not required vasopressors.

Effect of RBC transfusion on oxygenation variables: The determinants of SvO_2 involve SaO_2, VO_2, CO and Hb [$ScVO_2 \approx SvO_2 = SaO_2 - (VO_2 /CO*Hb*1.34)$]. Hence, the increase in $ScvO_2$ is well expected due to the significant increase in Hb and this even with the reduction of CO. Some authors report that the increase in $ScVO_2$ was rather noted with a low baseline $ScVO_2$. N Zeroual., *et al*. [15] in their study focused on cardiovascular surgery patients, demonstrated that the significant increase in $ScVO_2$ after transfusion was noted in the subgroup of patients with a baseline $ScVO_2 < 65\%$ with a specificity of 85%. Likewise, in a study conducted by RM Surve., *et al*. a significant increase in this parameter was noted (69.6 ± 11.5 vs 74.7 ± 8.9, $p < 0.001$), especially as the initial value was low [20]. In our series, we saw that $ScVO_2$ significantly increased 2 hours after ET in all the population and regardless the septic status. In contrary to our results, B Saugel., *et al*. [14] and BF Mazza., *et al*. (in septic patients), [23] did not find an increase in this parameter after transfusion. It has been suggested in the later study, that RBC transfusion in septic patients probably acts by improving blood volume and not by improving tissue oxygenation (consistent with what we found that ET has no effect on $ScVO_2$ in severely septic patients).

Fogagnolo A., *et al*. [24], in a recent prospective cohort study assessed the arterial-venous oxygen difference (A-V O_2diff) as indicator to identify patients who may benefit from transfusion. For patients classified in the "appropriate" strategy group (transfused when the A-V O_2diff > 3.7 mL or not transfused when the A-V O_2diff ≤ 3.7 mL), 90-day mortality was significantly lower(24 vs 44%, p = 0,004), SOFA score decreased more rapidly and acute kidney injury occurred likely less [24]. Hence, the authors concluded that transfusion therapy should be individualized according to the oxygen reserve and patients with higher A-V O_2dif are the most potential beneficiaries [24].

Concerning the CaO_2, B Saugel., *et al*. [14] and J Gramm., *et al*. [25] observed the same result as ours increase [(9.9 ml/dl vs 12 ml/dl, $p < 0.001$) [14]] and [(11.3 ml/dl vs 12.7 ml/dl, p = 0.004) [25]]. This is a perfectly expected result since CaO_2 is proportionally linear to the Hb level. Thus, the increase in Hb always increases CaO_2 (unless there is simultaneously a dramatic fall in SaO_2).

For oxygen delivery, there was no significant increase in contrast to the increase in CaO_2. Our finding was similar to J Gramm., *et al*. [25] that was attributed to the absence of change in cardiac output. An increase in DO_2 has been shown to be significant only when the oxygen uptake index was low before transfusion [26]. B Saugel., *et al*. [14] found a significant increase in DaO_2 (934 vs 1042 ml/min, p = 0.002). The considerable increase in CaO_2 in this study could explain the improved oxygen delivery despite the reduced CO (the increase was 2.3 ml/dl compared to 1.3 ml/dl of our series). The above cited mata-analysis [20] revealed an increase in O_2 delivery that was associated with an increase in oxygen consumption after transfusion, especially in patients with sepsis. Regarding the increase in O_2 delivery, it was likely due to an increase in arterial oxygen content (which was showed in almost all studies including ours). Authors of this meta-analysis

suggest that in patients with sepsis, ET has a possible greater effect on tissue oxygenation. However, the increase in O_2 delivery does not necessarily reflect an increase in local tissue oxygenation [20]. In our patients with septic shock, paradoxically to the decrease in DO_2 that we observed, lactates level trended to decrease. Our finding highlighted the role of vasopressors in improving oxygen consumption (VO_2) in septic patients likely more than CGR transfusion. Our data are consistent with those of to an old clinical trial [27] of E. Gilbert., *et al*. that assessed the response of increase in DO_2 using 3 therapeutic tools (fluid versus blood versus catecholamines) in septic patients. The authors found that VO_2 increased after fluid loading and after CGR transfusion only in septic patients with lactic acidosis [27]. The group receiving catecholamine exhibited a significant Increase in VO_2 regardless of the presence or not of anaerobic metabolism [27] [normal lactate (428 vs 572, $p < 0.01$) or high lactate (371 vs 492, $p < 0.001$)].

Strength and Limitation

The results of our study contribute to a measurable understanding of the effects of erythrocyte transfusion on advanced hemodynamic and peripheral oxygenation parameters.

However, all these data must be interpreted with caution considering the small size, the transfused volume (1 RBC concentrate) and timing of evaluation (2 Hours of transfusion). Perhaps these effects are not short term and will require evaluation beyond 2 hours or repeated over 24 hours.

Conclusion and Suggestions

RBC transfusion in ICU patients induced a significant decrease in cardiac output and despite the significant increase in hemoglobin and arterial oxygen content, the oxygen delivery (ultimate goal of erythrocyte transfusion) not changed. The presence of septic shock would rather decrease DO_2 and not changed $ScVO_2$. These findings deserve to be supported by large-scale studies in order to establish a reasonable transfusion strategy for each type of ICU patient.

Bibliography

1. Astin R., *et al*. "Anaemia secondary to critical illness: an unexplained phenomenon". *Extreme Physiology and Medicine* (2014): 4.

2. Corwin HL., *et al*. "The Crit study: anemia and blood transfusion in the critically ill-current clinical practice in the United States". *Critical Care Medicine* (2004): 39-52.

3. Vincent JL., *et al*. "Anemia and blood transfusion in critically ill patients". *The Journal of the American Medical Association* (2002): 1499-1507.

4. Ahsen N., *et al*. "Important role of non diagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients". *Critical Care Medicine* (2001): 2630-2639.

5. Weiss G., *et al*. "Anemia of chronic disease". *The New England Journal of Medicine* (2005): 1011-1023.

6. Hayden SJ., *et al*. "Anemia in critical illness: insights into etiology, consequences, and management". *American Journal of Respiratory and Critical Care Medicine* (2012): 1049-1057.

7. Hébert PC., *et al*. "Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care". *The New England Journal of Medicine* (1999): 409-417.

8. Corwin HL., *et al*. "Efficacy and safety of epoetin alfa in critically ill patients". *The New England Journal of Medicine* (2007): 965-976.

9. Cavalcante Dos Santos., *et al*. "How have red blood transfusion practices changed in critically ill patients? A comparison of the ICON and ABC studies conducted 13 years apart". *Transfusion* (2020): 2801-2806.

10. Hébert PC., *et al*. "Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group". *American Journal of Respiratory and Critical Care Medicine* (1997): 1618-1623.

11. Wu WC., *et al*. "Blood transfusion in elderly patients with acute myocardial infarction". *The New England Journal of Medicine* (2001): 1230-1236.

12. Gestion et prévention de l'anémie (hors hémorragie aigüe) chez le patient adulte de soins critiques Recommandations Formalisées d'Experts". *SFAR, SRLF* (2019).

13. Holst LB., *et al*. "Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis". *British Medical Journal* (2015): 350.

14. Saugel B., *et al*. "Effects of red blood cell transfusion on hemodynamic parameters: a prospective study in intensive care unit patients". *Scandinavian Journal of Trauma, Resuscitation* (2013): 21.

15. Zeroual N., *et al*. "ScvO2 changes after red-blood-cell transfusion for anemia in cardiothoracic and vascular ICU patients: an observational study". *Vox Sanguinis* (2018): 136-142.

16. Surve RM., *et al*. "The effect of blood transfusion on central venous oxygen saturation in critically ill patients admitted to a neurointensive care unit". *Transfusion Medicine* (2016): 343-448.

17. Mungayi V., *et al*. "Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit: a quasi experimental study". *African Journal of Emergency Medicine* (2014): 66-70.

18. Cornet AD., *et al*. "Pulmonary effects of red blood cell transfusion in critically ill, non-bleeding patients". *Transfusion Medicine* (2010): 221-226.

19. Sadaka F., *et al*. "The effect of red blood cell transfusion on tissue oxygenation and microcirculation in severe septic patients". *Annals of Intensive Care* (2011): 46.

20. Cavalcante Dos Santos E., *et al*. "Systematic Review and Meta-Analysis of Effects of Transfusion on Hemodynamic and Oxygenation Variables". *Critical Care Medicine* (2020): 241-248.

21. Roberts J., *et al*. "Oxygen delivery in septic shock". *Annals of the American Thoracic Society* (2015): 952-955.

22. Vincent JL., *et al*. "Restrictive versus more liberal blood transfusions? The answer is in your heart". *Minerva Anestesiologica* (2016): 511-513.

23. Mazza BF., *et al*. "Evaluation of blood transfusion effects on mixed venous oxygen saturation and lactate levels in patients with SIRS/sepsis". *Clinics* (2005): 311-316.

24. Fogagnolo A., *et al*. "Using arterial-venous oxygen difference to guide red blood cell transfusion strategy". *Crit Care* (2020): 160.

25. Gramm J., *et al*. "Effect of transfusion on oxygen transport in critically ill patients". *Shock* (1996): 190-193.

26. Casutt M., *et al*. "Factors influencing the individual effects of blood transfusions on oxygen delivery and oxygen consumption". *Critical Care Medicine* (2001): 173-179.

27. Gilbert EM., *et al*. "The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis". *The American Review of Respiratory Disease* (1986): 873-878.

Volume 5 Issue 7 July 2021