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Elmi Messaï
Abdesselam Bouguerra
Guy Harmelin
Gabriella Di Lascio
Giovanni Cianchi
Massimo Bonacchi

A new formula for determining arterial oxygen saturation during venovenous extracorporeal oxygenation

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E. Messaï (✉)
Service de réanimation, Centre hospitalier de Cholet, 1 rue Marengo BP 507, 49325 Cholet, France
e-mail: elmi.messai@ch-cholet.fr
Tel.: +33-2-41496398
Fax: 33-2-41496408

A. Bouguerra
Département de Physique, Université de Souk-Ahras, 41000 Souk-Ahras, Algeria

G. Harmelin · G. Di Lascio · M. Bonacchi
Cardiac Surgery, Medical and Surgical Critical Care Department, University of Florence, Florence, Italy

G. Cianchi
Anesthesia and Intensive Care Unit, Emergency Department, Careggi Teaching Hospital, Florence, Italy

Abstract *Purpose:* Venovenous extracorporeal membrane oxygenation (VV-ECMO) is used to treat severe forms of acute respiratory distress syndrome (ARDS). VV-ECMO management may be confusing due to the lack of information about the interplay between the determinant parameters and their impact on oxygenation. We found a relationship between arterial oxygen saturation (SaO_2) and its relevant parameters. The aim of this study was to assess the validity of this model. *Methods:* We report our experience in 17 patients under VV-ECMO for severe ARDS. We compared, at two different levels of pump flow, SaO_2 and the oxygen saturation measured in the pulmonary artery ($SpaO_2$) with the predicted saturation using the formula: $SpaO_2 = (EF/CO)SmO_2 + (1 - EF/CO)SvO_2 + 10^{-2}PmO_2$, where PF is pump flow, R is recirculation, EF is effective flow [= (1 − R)PF], SmO_2 is saturation of the oxygenator outgoing blood, CO is cardiac output, SvO_2 is saturation of mixed venous blood, and PmO_2 is oxygen partial pressure of the oxygenator outgoing blood. *Results:* There was no significant difference between predicted and measured $SpaO_2$: the mean predicted and measured $SpaO_2$ values were 90.7 ± 2.8 % and 90.4 ± 2.7 % , respectively ($p = 0.696$, $r = 0.966$). Bland-Altman analysis showed good agreement between predicted and measured $SpaO_2$. Predicted $SpaO_2$ and SaO_2 was well correlated ($r = 0.80$). *Conclusions:* We have presented an explicit relationship between SaO_2 and its direct determinants during VV-ECMO. Good agreement was found with the measured values of SaO_2, but the model remains to be fully validated before its use in clinical practice.

Keywords Acute respiratory distress syndrome · Oxygenation · ECMO · Recirculation

Introduction

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is used to treat the most severe forms of acute respiratory distress syndrome (ARDS) [1–5]. The objective of the VV-ECMO technique is to correct severely impaired gaseous exchange due to lung injury and to allow pulmonary recovery [6–8]. Normocarbia is easy to achieve but sufficient oxygenation is not always possible. The greater solubility of carbon dioxide (CO_2), coupled with the fact that the CO_2 dissociation curve is more linear and more steep than the oxygen (O_2) dissociation curve, imply that CO_2 clearance (and $PaCO_2$) are largely determined by the rate of fresh gas flow. But blood oxygenation is controlled by blood flow (or pump flow, PF) which depends on the patient's cardiac output (CO)

and the recirculation rate (R). Whereas effective oxygenation requires high PF values from 50–60 to 80–100 mL/kg/min, effective CO_2 clearance can be reached with values as small as 10–15 mL/kg/min [9, 10].

R is defined as the fraction of oxygenated blood that exits the infusion port and is immediately drained back into the drainage port, instead of being delivered to the patient's circulation. Recirculation is a dynamic event and R is influenced by a variety of factors, such as cannula position, volume status, PF rate, and CO. In the absence of recirculation, PF only needs to be equal to CO to achieve complete oxygenation. R increases with PF and is a recognized limiting factor in VV-ECMO [11, 12]. Moreover, there are other possible causes of decreased blood oxygenation during ECMO: for example, variation in a patient's CO, and an increase in a patient's O_2 consumption (e.g. sepsis, hyperthermia etc.).

This difficulty in achieving sufficient oxygenation explains: (1) saturation targets recommended by the VV-ECMO guidelines (for example, Extracorporeal Life Support Organization guidelines define adequate support as support allowing an arterial saturation greater than 80 % [13]), and (2) research to improve oxygenation by reducing recirculation (bicaval drainage [14] and the χ-configuration [15]).

The physiology of VV-ECMO is complex [9] and the absence of an explicit relationship between the determinants of oxygenation and the consequences of their interactions makes the management of oxygenation during VV-ECMO quite intricate [11, 16]. As in a similar mathematical description of the mixing of venous blood [17], we believe that mathematical modelling may be a valuable tool for exploring oxygenation during VV-ECMO, particularly the interplay between blood oxygenation and its delivery parameters. After validation, such a model could be useful in clinical practice: firstly, it could enable these parameters to be optimized and better adjusted when starting an ECMO procedure in order to achieve sufficient oxygenation, and secondly, these parameters could be corrected if hypoxaemia did indeed occur during VV-ECMO. From the physiology of transport and delivery of O_2 to tissues, we established a relationship between arterial O_2 saturation (SaO_2) and its determinants. The aim of this study was to validate this formula.

Patients and methods

Patient characteristics

From August 2007 to January 2012, 17 patients with ARDS were treated with VV-ECMO. All patients failed to reach an acceptable blood oxygenation level with optimized ventilation settings (inspired O_2 fraction >90 % and plateau airway pressure >30 cmH_2O) combined with supportive treatment (inhaled NO, prone positioning, etc.) as appropriate for each patient. The protocol was approved by the central institutional review board. All patients or their relatives signed informed consent forms. We applied the Extracorporeal Life Support Organization indications and contraindications to VV-ECMO [13].

ECMO management and patient interventions

We set up a standard two-cannula femorojugular VV-ECMO circuit (Fig. 1). Deoxygenated blood was drained from the right atrium through a cannula inserted into the right femoral vein. The oxygenated blood was restored via a short cannula inserted into the right internal jugular vein reaching the distal part of the superior vena cava. The sizes of cannulas were in the range 21–28F depending on the patient's anatomical features. The ECMO equipment used was a centrifugal pump (Rotaflow; Maquet, Hirrlingen, Germany) and a hollow fibre oxygenator (Quadrox-D; Maquet) connected with tubes treated with Bioline Coating (Maquet). The oxygenator's FiO_2 was set at 100 % and gas flow was set 1:1 with blood flow. Once optimal PF had been achieved (equal to 80 % of the patient's CO), ventilation was gradually reduced for protective ventilation [7]. Protective ventilation [18] settings were: pressure control, inspiratory plateau pressure of less than 30 cm H_2O, and positive end-expiratory pressure between 10 and 15 cm H_2O, depending on the pressure/volume curves. Respiratory frequency was reduced to 4–10/min. FiO_2 was reduced to 50 % or lower, whenever possible.

Patient monitoring

A pulmonary artery catheter was inserted in order to measure CO and to take pulmonary blood samples for gas analysis. Central venous blood gas analysis was obtained through a central venous catheter. Circuit monitoring included pre-oxygenator and post-oxygenator blood gas analysis and pressure analysis.

Formula for SaO_2 calculation

From physiology of transport and delivery of O_2 to tissues, we established a relationship between SaO_2 and its determinants:

$$SaO_2 \approx SpaO_2 = (EF/CO)\,SmO_2 + (1 - EF/CO)\,SvO_2 + \Delta SaO_2.$$

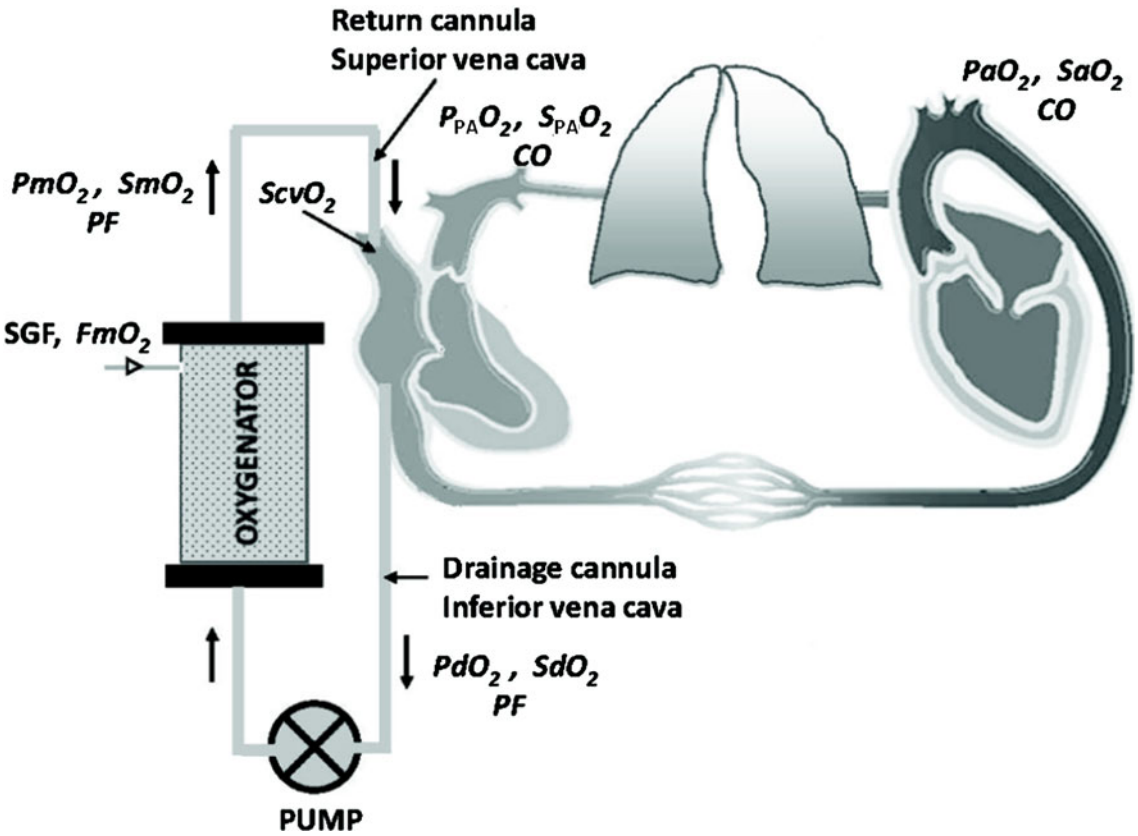

Fig. 1 VV-ECMO configuration: PdO_2 partial pressure of O_2 in the drainage cannula, SdO_2 O_2 saturation in the drainage cannula, *PF* pump flow, PmO_2 partial pressure of O_2 in the blood exiting the oxygenator (membrane), SmO_2 O_2 saturation in the blood exiting the oxygenator (membrane), $ScvO_2$ central venous O_2 saturation, *CO* cardiac output, *SGF* sweep gas flow, FmO_2 fractional inspired O_2 sweep gas, PaO_2 partial pressure of O_2 in the radial artery, SaO_2 O_2 saturation in the radial artery, $PpaO_2$ partial pressure of O_2 in the pulmonary artery, $SpaO_2$ O_2 saturation in the pulmonary artery

where $SpaO_2$ is the O_2 saturation in a pulmonary artery (%), EF = (1 − *R*) PF; EF is the effective flow rate (L/min), PF is the pump flow (L/min), *R* is the recirculation rate (%), SmO_2 is the O_2 saturation of the blood leaving the oxygenator (mm Hg), CO is the cardiac output (L/min), SvO_2 is the O_2 saturation of mixed venous blood (%), and ΔSaO_2 ($\approx 10^{-2}$ PmO_2; PmO_2 is the partial O_2 pressure of the blood leaving the oxygenator, mm Hg) is the increase in SaO_2 due to dissolved O_2 (%). Figure 1 shows the VV-ECMO configuration.

SvO_2 measurement

SvO_2 is the percentage of haemoglobin saturated with O_2 in mixed venous blood. Mixed venous blood is the mixture of blood from all regions of the body in the right cavities, before being oxygenated in the lung capillaries. SvO_2 can be obtained by taking a blood sample via a pulmonary artery catheter [19]. Under ECMO, the mixed venous blood is the last point in the circulation before oxygenation. Some of the mixed venous blood is withdrawn through the drainage cannula and passes through the oxygenator. The mixed venous blood that is not drained by the circuit flows through the pulmonary arteries without being oxygenated. Consequently, it is impossible to measure SvO_2 under VV-ECMO by sampling blood from the pulmonary artery, because the O_2 content of the blood entering the pulmonary circulation is a mixture of the deoxygenated venous return and the oxygenated blood from the circuit.

In all the calculations we replaced SvO_2 with $ScvO_2$ (superior vena cava O_2 saturation) which has a similar value to SvO_2, by sampling blood from a major vein that was not affected by the recirculation or by the blood resulting from the ECMO circuit. Central venous blood samples for gas analysis were obtained through a central venous catheter positioned in the distal portion of the superior vena cava [15, 19].

Recirculation calculation

For determination of *R*, we applied a simple formula, using the evaluation of blood O_2 saturation obtained from

Table 1 Pre-ECMO data

Parameter	Value
Patients (*n*)	17
Male, *n* (%)	13 (76)
Age (years)	42.6 ± 25.2
Body surface area (m^2)	1.96 ± 0.28
ARDS aetiology (*n*)	
Bacterial pneumonia	8
Viral pneumonia	6
Trauma/postoperation	2
Other	1
Mechanical ventilatory settings	
Ventilation support (days)	5.4 ± 2.5
Minute volume (mL/min)	10579 ± 1840
FiO_2 (%)	97 ± 1
Peak inspiratory pressure (cmH_2O)	43.8 ± 9.6
PEEP (cmH_2O)	12.7 ± 3.1
Pulmonary compliance (mL/cmH_2O)	12.3 ± 7.4
Oxygenation index	59.4 ± 11.2
Murray score	3.3 ± 0.80
Arterial blood gas values	
pH	7.23 ± 0.08
$PaCO_2$ (mmHg)	76.4 ± 13.2
PaO_2 (mmHg)	59.2 ± 2.8
SaO_2 (%)	79.2 ± 6.6
PaO_2/FiO_2 ratio	59 ± 2.5
Haemodynamic values	
Systolic blood pressure (mmHg)	121 ± 22
Diastolic blood pressure (mmHg)	63 ± 14
Pulmonary artery systolic pressure (mmHg)	41 ± 13
Pulmonary artery diastolic pressure (mmHg)	23 ± 9
Pulmonary artery occlusion pressure (mmHg)	13 ± 6
Cardiac index ($L/min/m^2$)	3.1 ± 1.5
Survival on discharge, *n* (%)	
Intensive care unit	10 (58.8)
Hospital	9 (53)

Values are means ± standard deviation
FiO$_2$ fraction of inspired O_2, *PEEP* positive end-expiratory pressure, *PaCO*$_2$ arterial carbon dioxide tension, *PaO*$_2$ arterial oxygen tension, *SaO*$_2$ arterial oxygen saturation

Table 2 VV-ECMO data at ECMO flow 80 % of CO

Parameter	Value
Ventilator settings	
FiO_2 (%)	36.8 ± 12.6
Respiratory minute volume (mL)	1945 ± 685
Tidal volume (mL)	182 ± 112
Breaths per minute	8.2 ± 4.7
PEEP (cmH_2O)	11.6 ± 3.4
Peak inspiratory pressure (cmH_2O)	29.3 ± 7.1
Haemodynamic values	
Cardiac output (L/min)	7.42 ± 1.33
Cardiac index (m^2/L/min)	3.77 ± 1.4
VV-ECMO settings	
ECMO flow (L/min)	5.68 ± 1.04
ECMO gas flow (L/min)	6.5 ± 1.8
ECMO FiO_2 (%)	100
Radial artery blood samples	
pH	7.45 ± 1.7
PCO_2 (mmHg)	33.4 ± 4.6
PO_2 (mmHg)	85.3 ± 19.5
SO_2 (%)	95.7 ± 1.7
Haemoglobin concentration (g/dL)	12.7 ± 4.6
Pulmonary artery blood samples	
pH	7.42 ± 0.196
PCO_2 (mmHg)	39.8 ± 6.2
PO_2 (mmHg)	83.8 ± 14.7
SO_2 (%)	92.3 ± 2.4
Central venous samples	
pH	7.28 ± 1.2
PCO_2 (mmHg)	52.1 ± 3.1
PO_2 (mmHg)	40.1 ± 5.4
$ScvO_2$ (%)	74.5 ± 3.6
Pre oxygenator samples	
PCO_2 (mmHg)	46.3 ± 4.8
PaO_2 (mmHg)	48.6 ± 5.7
SO_2 (%)	82.5 ± 7.2
Post oxygenator samples	
PCO_2 (mmHg)	31.7 ± 9.2
PO_2 (mmHg)	457 ± 83.1
SO_2 (%)	99.8 ± 0.4
Recirculation rate (%)	28.8 ± 7.9
Time on ECMO (h)	323.6 ± 121.8

Values are means ± standard deviation
FiO$_2$ fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *PCO*$_2$ carbon dioxide tension, *PO*$_2$ oxygen tension, *SO*$_2$ oxygen saturation, *ScvO*$_2$ central venous oxygen saturation

different sites according to the formula [15]: $R\ (\%) = (SdO_2 - SvO_2)/(SmO_2 - SvO_2) \times 100$, where SdO_2 is the O_2 saturation in the drainage cannula, SmO_2 is the O_2 saturation level of the blood exiting the oxygenator (membrane), and SvO_2 is the O_2 saturation of the mixed venous blood.

Data collection and statistical analysis

Blood samples were collected from the patient's radial artery, pulmonary artery, central venous catheter, pre-oxygenator and post-oxygenator lines when the ECMO PF was 80 % of CO and protective mechanical ventilation was used. A second measurement was obtained when the ECMO PF was reduced to 50 % of CO during weaning from the support. Every measurement was repeated three times. Any individual measurement at any site that differed by more than 10 % from the other two measurements was discarded and another measurement was obtained. The respective mean values were analysed. *R* was calculated in all patients from the gasometric data. $SpaO_2$ was inferred from the formula and then compared to the measured value from the blood samples. Data collection and statistical analysis were conducted with XLSTAT. The normality of the distribution parameters was verified with the Kolmogorov-Smirnov test. The *t* test was used to compare data between the two groups. Data were analysed using Bland-Altman plots. The results are presented as means ± standard deviations and *p* values <0.05 were considered significant.

Results

Pre-ECMO data are shown in Table 1, and include demographic data, body surface area, ARDS aetiology, mechanical ventilatory settings, arterial blood gas values, haemodynamic values, survival at intensive care unit discharge and on hospital discharge. VV-ECMO data are presented in Table 2.

VV-ECMO assessment started after the patient had been stabilized (9.59 ± 6.2 h). We obtained measurements in each patient when the following conditions were fulfilled: PF was 80 % of the patient's CO, SaO_2 was ≥90 % and protective pulmonary ventilation was sufficient (mean peak inspiratory pressure 29.3 ± 7.1 cm H_2O, respiratory minute volume 1945 ± 685 mL, tidal volume 182 ± 112 mL, FiO_2 36.8 ± 12.6 %). A second set of measurements was obtained during weaning from ECMO, when PF was 50 % of CO. The results of the $SpaO_2$ calculation are presented in Table 3.

When PF was 80 % of CO, the mean PF was 5.68 ± 1.04 L/min and *R* was 28.8 ± 7.9 %. $SpaO_2$ values were in the range 88.7–96.8 %. Mean measured $SpaO_2$ was 92.3 ± 2.4 % and mean predicted $SpaO_2$ was 92.8 ± 2.3 % (not significantly different, $p = 0.513$). The O_2 saturation was significantly lower in the pulmonary artery than in the radial artery (SaO_2; 92.8 ± 2.4 versus 95.7 ± 1.7 %, $p < 0.002$), and the predicted $SpaO_2$ and SaO_2 were well correlated ($r = 0.80$). When PF was 50 % of CO, the mean PF was 3.25 ± 0.44 L/min and *R* was 9.2 ± 2.5 %. $SpaO_2$ values were in the range 85.1–91.1 %. Mean measured $SpaO_2$ was 88.5 ± 1.38 % and mean predicted $SpaO_2$ was 88.6 ± 1.5 % (not significantly different, $p = 0.888$).

Figure 2 shows the statistical analysis. In two series (34 measurements), $SpaO_2$ values were in the range 85.1–98 %. Mean predicted $SpaO_2$ was 90.7 ± 2.8 % and mean measured $SpaO_2$ was 90.4 ± 2.7 % (not significantly different, $p = 0.696$). So predicted $SpaO_2$ values and measured $SpaO_2$ values were well correlated ($r = 0.966$). Bland-Altman analysis showed that predicted $SpaO_2$ value were close to measured $SpaO_2$ values with a low bias (0.271 ± 0.736 %) and the limits of

Table 3 $SpaO_2$ calculation. 1–17 are values corresponding to a PF of 80 % of CO and 18–34 are values corresponding to a PF of 50 % of CO

	R (%)	SmO_2 (%)	PF (L/min)	CO (L/min)	$ScvO_2$ (%)	PmO_2 (mmHg)	$SpaO_2$	
							Calculated	Measured
1	26.7	100	4	5.6	74	560	93.2	92.6
2	39.6	100	6.4	8	70.3	450	89.2	88.7
3	28.9	99	5.8	7.8	69.5	410	89.2	88.9
4	18.5	100	5	7.2	73	540	93.7	94
5	26.5	100	5	6.4	79	430	95.4	96
6	30.6	99	6	8.2	74	505	91.7	90.9
7	29.3	100	5.2	6.5	77	575	95.8	94.8
8	17.9	100	4.5	5.7	82	430	98	96.8
9	19.9	100	5	6.5	69	310	91.2	89.7
10	36.8	99	6.2	8.4	76	585	92.6	92.8
11	42.1	100	8	10.4	78	340	91.2	90.8
12	37.5	100	4.2	5.2	74	460	91.7	90.8
13	19.9	99	5.8	8.2	72	420	91.5	90.5
14	36.9	100	7.2	9	78	320	92.3	91.5
15	25.7	100	6	7.8	76	450	94.2	94.6
16	32.4	100	6.4	8	74	480	92.9	92.7
17	19.7	100	5.8	7.3	70	500	94.1	93.8
18	10.2	99	3	5.2	72	310	89.1	88.5
19	11.5	100	3.5	6.5	71	280	87.6	86.8
20	12.6	100	4	7.2	72.1	260	88.2	89
21	9.6	99	3.4	6.5	71.3	280	87.2	87.6
22	6.3	99	3	6	73	260	87.8	86.9
23	8.6	99	3.2	6.5	75	290	88.7	89.4
24	11.3	100	3.5	6	73	300	90.0	88.5
25	6.5	100	3.2	6	75	250	90.0	90.4
26	5.9	99	2.5	5.5	71	210	85.8	86.3
27	9.4	100	3	6.2	75	270	88.7	87.8
28	12.8	100	3.6	6.8	71	260	87.0	87.3
29	12	100	3	5	72	220	89.0	90.2
30	4.2	99	3.4	5.6	74	240	90.9	90.2
31	9.6	100	2.5	6	77	190	87.6	87.3
32	8.5	99	2.8	5.6	74	310	88.5	89.1
33	10.1	100	3.6	6.6	77	280	91.1	90.8
34	7.2	100	4	7.2	73	260	89.5	88.7

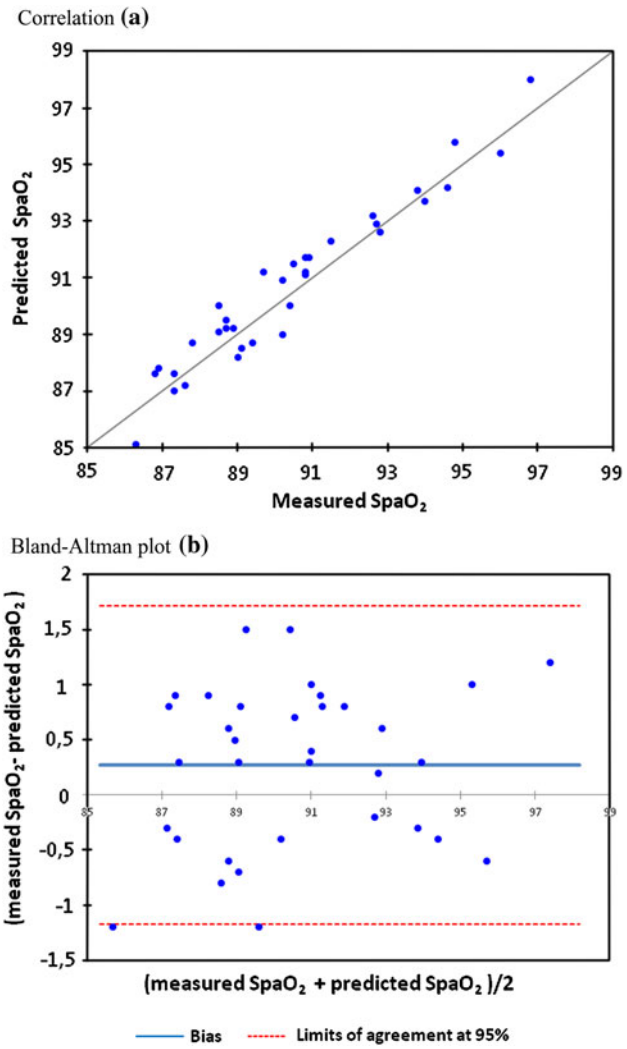

Fig. 2 Statistical analysis. **a** Correlation between predicted $SpaO_2$ and measured $SpaO_2$. **b** Bland-Altman plot of the difference between predicted $SpaO_2$ and measured $SpaO_2$, showing the bias as the mean difference and the limits of agreement at 95 % as the mean difference ±2 SD

agreement at 95 % were in the clinically acceptably range (−1.17 % to +1.71 %). Thus, when oxygenation is adequate, measured and predicted $SpaO_2$ values are in good agreement.

Discussion

VV-ECMO is used to treat the most severe forms of acute respiratory failure. However, sufficient blood oxygenation with VV-ECMO remains difficult to achieve [10, 11, 16, 20]. Oxygenation depends on many parameters including CO and *R* [9, 10]. We established a new relationship between SaO_2 and the relevant parameters under VV-ECMO. The focus of the study was to validate this relationship in relation to the treatment of ARDS.

Our main finding was that there is a good match between $SpaO_2$ as predicted by the formula and $SpaO_2$ as measured at two levels of PF (predicted $SpaO_2$ 90.7 ± 2.8 versus measured $SpaO_2$ 90.4 ± 2.7 %, $p = 0.696$. SaO_2 is mainly determined by the saturation of the blood before passing through the lungs ($SaO_2 \approx SpaO_2$). In our study, $SpaO_2$ was lower than SaO_2 because the residual pulmonary function helps increase the oxygenation level. However, we were able to demonstrate a good correlation between predicted $SpaO_2$ and SaO_2 ($r = 0.80$).

Two approximations may cause a lack of precision when predicting $SpaO_2$. First, $ScvO_2$ is an approximation of SvO_2, and the relationship between these two variables changes with catheter placement and CO, and can be influenced by relative changes in superior and inferior vena cava flow and coronary sinus flow. Placement of the tip of the central line near the right atrium (in our study, in the distal portion of the superior vena cava) increases the accuracy of $ScvO_2$ in reflecting SvO_2 [15, 19]. Second, ΔSaO_2 is an approximate value which depends on many parameters, including haemoglobin saturation in the right heart cavities (mixture of saturated haemoglobin from the oxygenator and unsaturated haemoglobin), CO, PF, *R*, PmO_2, haemoglobin concentration, and haemoglobin affinity for O_2. Increased accuracy is possible, but the formula becomes too complex for clinical use.

Moreover, SaO_2 can be lower than $SpaO_2$ for the following reasons: (1) in a normal lung, some of the bronchial artery blood is collected by the pulmonary veins after perfusing the bronchi and its O_2 is partly depleted, (2) a small amount of coronary venous blood drains directly into the cavity of the left ventricle through the Thebesian veins, and (3) some patients have an abnormal vascular connection between the small pulmonary artery and vein (pulmonary arteriovenous fistula) [21]. The role of each relationship determinant (SmO_2, PmO_2, PF, *R*, CO and SvO_2) in the oxygenation was confirmed. According to current recommendations, recapitulated in guidelines and troubleshooting charts [11, 16] and also deduced from the formula, hypoxaemia may occur for the following reasons: low SmO_2 and low PmO_2 (failure of oxygenator), high *R* (decrease in EF), elevated CO (decrease in the EF/CO ratio), and low SvO_2 (increase in the relative contribution of deoxygenated blood to oxygenation).

Although the information contained in this formula corroborates all the current recommendations in the event of insufficient oxygenation under ECMO [11, 16], we are aware of its limitations. It has only been tested over a normal oxygenation range. If these results are reproducible in situations of insufficient oxygenation, this formula may be useful in the clinical context. In practical terms, if blood oxygenation is insufficient or if hypoxaemia occurs during VV-ECMO, collecting all the parameters of the

equation might allow the clinician to analyse the cause and address the deficiency promptly.

Conclusions

The use of VV-ECMO in patients suffering from severe acute respiratory failure has increased in advanced critical care medicine. However, in a certain number of cases, it is impossible to obtain a sufficient SaO_2, and VV-ECMO management may be confusing. In this paper we have presented a new and explicit relationship between SaO_2 and its direct determinants. This model sheds new light on oxygenation during VV-ECMO and allows a good grasp of oxygenation physiology when using this technique. To the best of our knowledge, there are no explicit results in the literature regarding how the important determinant parameters interact and affect oxygenation. Previous work has been limited to recommendations recapitulated in guidelines or troubleshooting charts. We validated the relationship under conditions of sufficient oxygenation, and a greater oxygenation range needs to be examined to complete the validation of the model. Despite this, we believe our work could be a starting point for a new way to use VV-ECMO.

Conflicts of interest None of the authors has a source of support or a relationship with a commercial entity that has an interest in the subject of this article.

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