Review Article

Oxygenator performance and artificial-native lung interaction

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Abstract: During extracorporeal membrane oxygenation (ECMO), oxygen (O_2) transfer ($V'O_2$) and carbon dioxide (CO_2) removal ($V'CO_2$) are partitioned between the native lung (NL) and the membrane lung (ML), related to the patient's metabolic-hemodynamic pattern. The ML could be assimilated to a NL both in a physiological and a pathological way. ML O_2 transfer ($V'O_2ML$) is proportional to extracorporeal blood flow and the difference in O_2 content between each ML side, while ML CO_2 removal ($V'CO_2ML$) can be calculated from ML gas flow and CO_2 concentration at sweep gas outlet. Therefore, it is possible to calculate the ML gas exchange efficiency. Due to the ML aging process, pseudomembranous deposits on the ML fibers may completely impede gas exchange, causing a "shunt effect", significantly correlated to $V'O_2ML$ decay. Clot formation around fibers determines a ventilated but not perfused compartment, with a "dead space effect", negatively influencing $V'CO_2ML$. Monitoring both shunt and dead space effects might be helpful to recognise ML function decline. Since ML failure is a common mechanical complication, its monitoring is critical for right ML replacement timing and it also important to understand the ECMO system performance level and for guiding the weaning procedure. ML and NL gas exchange data are usually obtained by non-continuous measurements that may fail to be timely detected in critical situations. A real-time ECMO circuit monitoring system therefore might have a significant clinical impact to improve safety, adding relevant clinical information. In our clinical practise, the integration of a real-time monitoring system with a set of standard measurements and samplings contributes to improve the safety of the procedure with a more timely and precise analysis of ECMO functioning. Moreover, an accurate analysis of NL status is fundamental in clinical setting, in order to understand the complex ECMO-patient interaction, with a multi-dimensional approach.

Keywords: Extracorporeal membrane oxygenation (ECMO); oxygenator, membrane; monitoring, device; oxygen, delivery; carbon dioxide, removal

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Introduction

While its use is largely increasing, extracorporeal membrane oxygenation (ECMO) management has considerably changed based on research findings and technological progress (1), with increasing and remarkable short (2) and long-term (3,4) survival rates.

In veno-venous ECMO (VV ECMO) configuration, oxygen (O_2) transfer and carbon dioxide (CO_2) removal are provided by a membrane lung (ML), with its blood pump, placed in series with the failing native lung (NL). Therefore, the patient's lung physiologic gas exchange function can be totally or partially substituted by an artificial one.

During VV ECMO, the total amount of O_2 delivery

Table 1 Comparison of native lung (NL) and membrane lung (ML) features

Parameter	Native lung[#]	Membrane lung[^]
Alveolar-capillary exchange surface (m^2)	100–150	1.81
Exchange surface/blood volume (cm^{-1})	300	8
Alveolar-capillary membrane thickness (μm)	1–2	10–30
VO_2 (mL/min)	200–250 (at rest); 2,000–2,500 (on exercise)	0–350

[#], NL data from Chauhan S, Subin S. Extracorporeal membrane oxygenation, an anesthesiologist's perspective: physiology and principles. Part 1. Ann Card Anaesth 2011;14:218-29. [^], ML data from ECMO Adult Long Term Oxygenator Module Technical Characteristic (EUROSETS S.r.l., Medolla, MO, Italy).

and the total CO_2 removal cannot simply only rely on a two-dimensional relationship between NL ventilation and the patient's metabolic-hemodynamic pattern. A three-dimensional approach is then required, taking extracorporeal oxygenator gas exchange also into account. Therefore ML, NL and metabolic status should be analysed separately, in order to better understand their interaction and to correctly manage the patient-ECMO system.

Monitoring ML function and comparing it with the patient NL status are then important to understand the ECMO system performance level, in order to identify and correctly treat blood gas abnormalities and guiding the weaning procedure. Since ML failure is the second most common mechanical complication (5), its monitoring is crucial in order to recognise the right timing for ML replacement. ML gas exchange data are usually obtained by blood samplings from the ECMO circuit, for gas analysis, combined with simultaneous extracorporeal system measurement, during periodical ECMO system checks. Even if scheduled to prevent or detect problems that might arise during the treatment, these non-continuous assessments, however, may fail timely detection of critical issues. Considering the severity of the underlying disease and all of the risks connected with extracorporeal circulation, a continuous monitoring of ECMO systems might be an important step forward, by improving safety and adding relevant clinical information.

The present article deals with the clinical impact of an ECMO circuit monitoring system. The continuous examination of a set of critical parameters could represent an innovative way to monitor ML performance and the complex interaction with NL, together with important clinical inferences.

ML physiology and pathology

The oxygenator plays a central role during VV ECMO, replacing patient pulmonary alveolar function, as its main functions are to transfer O_2 to the blood ($V'O_2ML$) and to remove CO_2 ($V'CO_2ML$).

Non-microporous polymethylpentene hollow-fiber membranes are today mainly used for long-term ECMO application so that gas exchange is guaranteed, in a physiological way, by the partial pressure gradient on both sides of a diffusion membrane, without any direct gas-blood interface. Despite working in a similar way, NL and ML are different in terms of exchange surface area and membrane thickness (*Table 1*), thus limiting the maximal $V'O_2ML$ to 350 mL/min compared to the NL O_2 transfer ($V'O_2NL$), which could reach 2,500 mL/min during exercise (6).

Even from a pathological point of view, ML could be assimilated to a NL: according to Riley's three-compartment lung model (7), the oxygenator can be imagined as divided into functional units, characterized by different ventilation/perfusion (VA/Q) ratios (8). The ideal situation is represented by the absence of any coupling alterations between ventilation and perfusion (VA/Q =~1). Despite introduction of tip-to-tip antithrombotic surface coatings, the non-biologic surface of an extracorporeal circuit leads to a systemic inflammatory response, triggering the activation and consumption of pro- and anti-coagulant blood components (9), with thrombotic, fibrin or cellular deposits on hollow-fibers that worsen gas exchange performance (10). Extensive clot formation around fibers determines a ventilated but not perfused compartment, with a "dead space effect" (VA/Q =∞), while pseudomembranous deposits on fiber walls may completely impede gas exchange, causing a "shunt effect" (VA/Q =0).

ML oxygen transfer

$V'O_2ML$ (mL/min) is proportional to blood flow (BF, L/min) and the difference in O_2 content between blood coming out

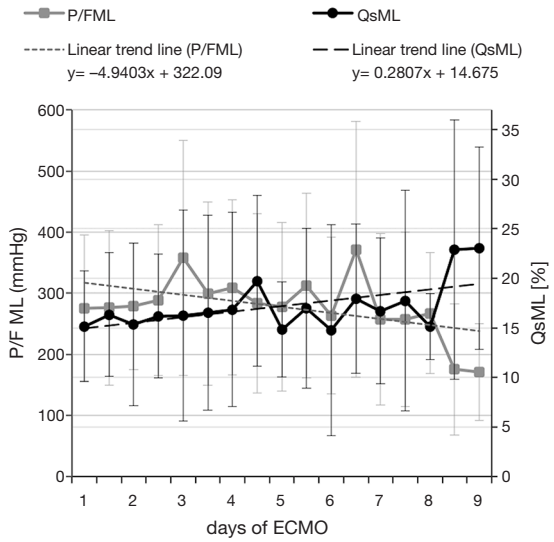

Figure 1 Inversely proportional relationship between membrane lung (ML) P/F ratio (P/FML—calculated as oxygen partial pressure at ML blood outlet to oxygen fraction ratio at ML gas inlet) and membrane lung shunt fraction (QsML). We collected data of 6 different MLs, every 12 hours, considering a 9-day ECMO-run length. We observed an increase of mean QsML, which ranged from 15.15%±5.58% to 23.2%±10.20%, and a contemporary decrease of P/FML, from a value of 275.58±119.09 to 170.79±79.16 mmHg. ECMO, extracorporeal membrane oxygenation. P/F ratio, PaO2/FIO2.

($C_{post}O_2$, mL/dL) and entering ($C_{pre}O_2$, mL/dL) the ML. It can be calculated as follows (8):

$$V'O_2ML = BF \times \left(C_{post}O_2 - C_{pre}O_2\right) \times 10$$

Since blood content in O_2 (C_aO_2) could be calculated as follows:

$$C_aO_2 = p_aO_2 \times 0.0031 + Hb \times SO_2 \times 1.34$$

it is easy to understand that haemoglobin concentration (Hb, g/dL) and its O_2 saturation (SO_2, %) are of paramount importance in the amount of O_2 carried by blood, while O_2 blood partial pressure (p_aO_2, mmHg) has a negligible role, represented by a very low (0.0031) solubility coefficient.

These formulas are representative of the several factors that are implied in the patient's oxygenation during VV ECMO support. Firstly, BF and ML gas inlet O_2 fraction ratio (F_iO_2ML) are crucial for blood oxygenation (11,12). The latter determines sweep gas O_2 partial pressure, which generates the O_2 pressure gradient that drives O_2 transfer. VV ECMO performance can be negatively affected by recirculation (13), caused by a fraction of oxygenated blood delivered by the infusing cannula withdrawn by the draining cannula, before entering the systemic circulation. Nonetheless the oxygenation power depends by ML intrinsic properties (surface area, hollow fiber thickness and composition) and ML performance, influenced by inlet blood venous saturation (14) and the age of the oxygenator itself.

Considering extracorporeal BF, it is obvious that only the portion coupled with ventilation is significant for blood oxygenation. Hence the importance of ML shunt fraction (Q_s/Q_{BF}) for O_2 transfer efficiency: the higher the shunt ratio, the lower the $V'O_2ML$. New ML have a negligible shunt ratio, theoretically lower than 10% (15), expected to increase because of ML aging process, as debris and fibrin coat the capillaries in which the blood flows, thus hindering the passage of O_2.

ML shunt can be calculated as follows (16):

$$\frac{Q_s}{Q_{BF}} = \frac{\left(C_{cap}O_2 - C_{post}O_2\right)}{\left(C_{cap}O_2 - C_{pre}O_2\right)}$$

where $C_{cap}O_2$ is to be considered as the ML capillary (ideal) O_2 concentration. It could be calculated with the O_2 blood content formula:

$$C_{cap}O_2 = 0.0031 \times p_iO_2 \times Hb \times SO_2$$

using $[100 - (HbCO + HbMet)]$ for SO_2 and

$$[(P_{ATM} - P_{H2O}) \times F_iO_2ML - p_aCO_2/RQ]$$

as p_iO_2. In the previous formulas Hb*CO* is Hb saturated in carbon monoxide, Hb*Met* is methemoglobin, p_iO_2 is oxygen partial pressure at ML gas inlet, P_{ATM} is atmospheric pressure, P_{H2O} is steam partial pressure, p_aCO_2 is blood CO_2 partial pressure and RQ is the respiratory quotient.

Though interesting in a speculative way, it is not surprising that shunt ratio is not widely used, as a trouble shouting parameter due to its cumbersome calculation. ML oxygenation performance is therefore commonly evaluated by ML P/F ratio (mmHg), calculated as O_2 partial pressure at ML blood outlet ($p_{post}O_2$, mmHg) to F_iO_2ML (ratio). ML P/F and Q_s/Q_{BF} ratios are therefore inversely proportional (*Figure 1*).

Even if ML P/F ratio is clearly a much more "user friendly" parameter, it has been demonstrated that the ML shunt only correlates significantly with its performance (17) and aging process. In fact, an abrupt and significant drop of ML P/F could occur without any evidence of ML impairment, for example with a low inlet blood O_2 saturation, in case of high metabolic demand (16).

ML carbon dioxide removal

VV ECMO has an enormous capacity to remove CO_2 from patient's blood. The ML gas flow (GF) is the major determinant of ML CO_2 removal (V'CO_2ML), which is relatively independent from BF (18). The increase of GF reduces the CO_2 partial pressure at ML sweep gas outlet (p_eCO_2), increasing the partial pressure gradient in between blood and gas phase and consequently augmenting V'CO_2ML.

V'CO_2ML (mL/min) can be easily calculated (19) from the ML GF (mL/min) and the CO_2 concentration at ML sweep gases outlet ($[CO_2]_e$, ratio), measured with an infrared analyser, as follows:

$$V'CO_2ML = GF \times [CO_2]_e$$

The infrared capnometer sampler must not impose great resistance in order to avoid pressure increase in the ML. A correct measurement can be obtained after at least 30 seconds of purge with high GF (10 L/min) in order to get rid of excessive moisture, as condensation and water vapour when trapped into hollow-fibers reduce ML decarboxylation capacity (20).

V'CO_2ML power is directly proportional to GF, as in the NL CO_2 elimination (V'CO_2NL), which is proportional to alveolar ventilation. Ventilated but not perfused ML sections, as it can occur when hollow-fibers are completely clogged with thrombi, do not participate to decarboxylation, generating the so-called ML dead space (VdsML, ratio). It can be calculated as follows (8):

$$VdsML = \frac{(p_{post}CO_2 - p_eCO_2)}{p_{post}CO_2}$$

obtained from CO_2 partial pressure at the ML blood outlet ($p_{post}CO_2$, mmHg) and p_eCO_2, (mmHg), also measured with an infrared CO_2 analyser at sweep gas outlet.

Therefore, VdsML negatively influences V'CO_2ML and it is compensated in clinical practice by a progressive increase of GF, in order to maintain a normal patient p_aCO_2.

Gas exchange partitioning

In VV ECMO configuration, since the extracorporeal ML is positioned in series to the patient's NL, the blood returning to the right heart (mixed venous blood), with its O_2 content ($C_{vmix}O_2$), is an admixture of the deoxygenated venous return and the well-oxygenated extracorporeal blood (8).

Depending on its residual function, the NL then adds an amount of O_2 (V'O_2NL), directly proportional to cardiac output (CO), calculated as follows:

$$V'O_2NL = CO \times (C_aO_2 - C_{vmix}O_2)$$

The final arterial C_aO_2 is afterwards the result of the total amount of O_2 transfer (V'O_2), partitioned into V'O_2ML and V'O_2NL:

$$V'O_2 = V'O_2ML + V'O_2NL$$

In a similar way, the total amount of CO_2 removal (V'CO_2) from the patient's blood could be partitioned into V'CO_2ML and V'CO_2NL:

$$V'CO_2 = V'CO_2ML + V'CO_2NL$$

Once in the pulmonary capillaries, CO_2 readily diffuses to the alveolar space, passing through the alveolar-capillary membrane in an extremely efficient way, that CO_2 alveolar partial pressure (p_ACO_2) usually can be considered to be equal to that of the pulmonary end-capillary blood. Hence, p_ACO_2 is the main important determinant of V'CO_2NL. Alveolar ventilation is then fundamental to compensate the continuous CO_2 supplement to alveolar gas from pulmonary circulation, by reducing p_ACO_2.

NL and ML gas exchange monitoring

During VV ECMO there is cooperation between the ML and the NL in gas exchange since these two systems work in-series. How V'O_2 and V'CO_2 are shared differently, depends on ML and NL functional states and ECMO and mechanical ventilation settings.

In order to evaluate all these data in their complexity, most centres use homemade electronic data sheets to collect raw data and calculate derived parameters of extreme importance, even though these informations are not continuous or calculated in real-time. Collecting these data can be cumbersome and time consuming. It is nonetheless important for a clear trend perception of ML performance and an estimation of the NL conditions and recovery. By this way it is possible to calculate ML Q_s/Q_{BF} and VdsML, at least daily or whenever clinical trends dictate the need for an accurate gas exchange assessment.

Many ECMO centres are investigating different ways for a real-time continuous system of monitoring. In our intensive care unit (ICU) of a tertiary university hospital, we use a monitoring system originally designed for short-term applications on heart-lung machines, in order to guide the

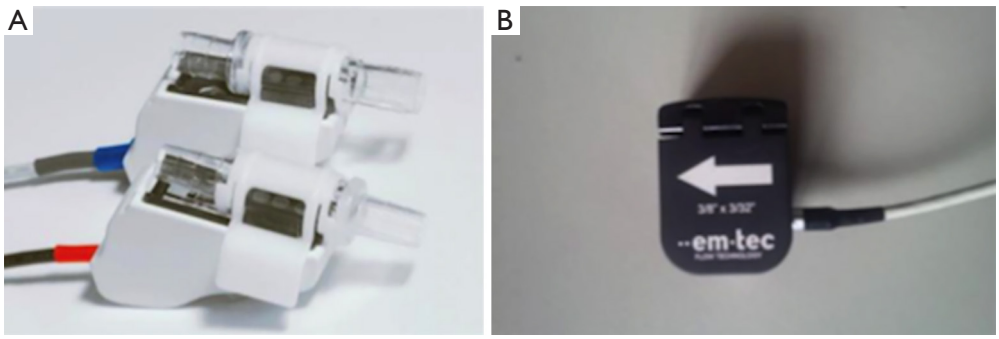

Figure 2 The two oxymetric probes (on the left, A) and the flowmeter (on the right, B) of the real-time extracorporeal circuit monitoring system in use in our ICU (Landing® Real Time Monitor, EUROSETS S.r.l., Medolla, MO, Italy).

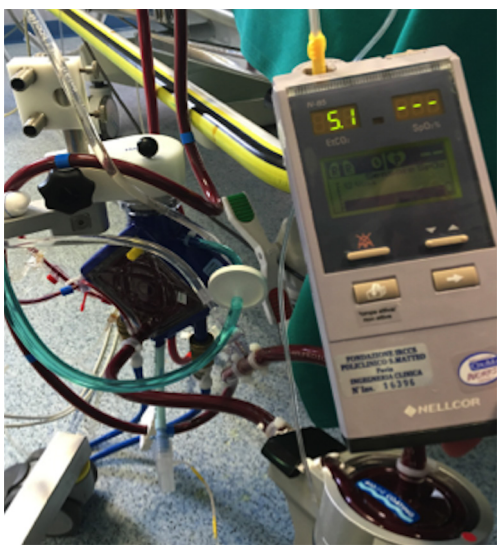

Figure 3 CO_2 percentage concentration measurement at ML sweep gases outlet, with the infrared analyser in use in our ICU [Nellcor™ N-85 Monitor (with OxiMax™ Technology & Microstream™ Capnography), MEDTRONIC, Minneapolis, MN, USA].

medical team in making decisions about cardiopulmonary bypass management. It provides information about O_2 transport and consumption, venous and arterial oxygenation, as well as extracorporeal circuit pressures and BF, with a capability to update data every 5 seconds and show their trends continuously. For its use it is necessary to make two cuts in the drainage and the reinfusion lines, in order to insert two specific 3/8" adapters for the probes (*Figure 2A*). Probe A, denoted as the venous probe, provides Hb concentration, pre-oxygenator (venous) Hb O_2 saturation (S_vO_2) and temperature (T_{ven}) measurements. Probe B, denoted as the arterial probe, provides the measurement of post-oxygenator (arterial) Hb O_2 saturation (S_aO_2) and temperature (T_{art}). An ultrasound flow meter provides the measurement of extracorporeal BF (*Figure 2B*). The monitor also manages three pressure transducers, connected to the ECMO circuit ports: pre-pump (drainage pressure), pre-ML (pre-oxygenator pressure) and post-ML (post-oxygenator pressure).

It calculates several derived parameters from measured values, and among them $V'O_2ML$ maintains validity during VV ECMO. It is calculated according to the following simplified equation (21):

$$V'O_2ML = BF \times (k \times Hb \times S_aO_2 - k \times Hb \times S_vO_2)$$

using a coefficient (k = 13.8), for $V'O_2ML$ expressed as mL/min, Hb as *g/dl* and BF as L/min.

The $V'O_2NL$ measurement is performed rarely, because it requires a pulmonary artery catheter, not commonly used in our ICU, except for particular selected cases.

Besides these continuous measurements, we also perform measurements of the decarboxylation function of the NL and ML. $V'CO_2NL$ is obtained by the volumetric capnometry function integrated into our mechanical ventilator. $V'CO_2ML$ is calculated at least on a daily basis by volumetric capnometry, applied to the ML, with an infrared CO_2 analyser at the sweep gas outlet (*Figure 3*).

The measured values are reliable and reasonably accurate, but obviously the system has some limits. First of all, it represents an adjunct to our daily ECMO analysis, but it cannot substitute it completely. Blood samples must be obtained daily also to calibrate the machine and we have to refer to blood samples every time we consider that the values have changed or the clinical situation does not reflect what we see on the screen. The system aims in casting some

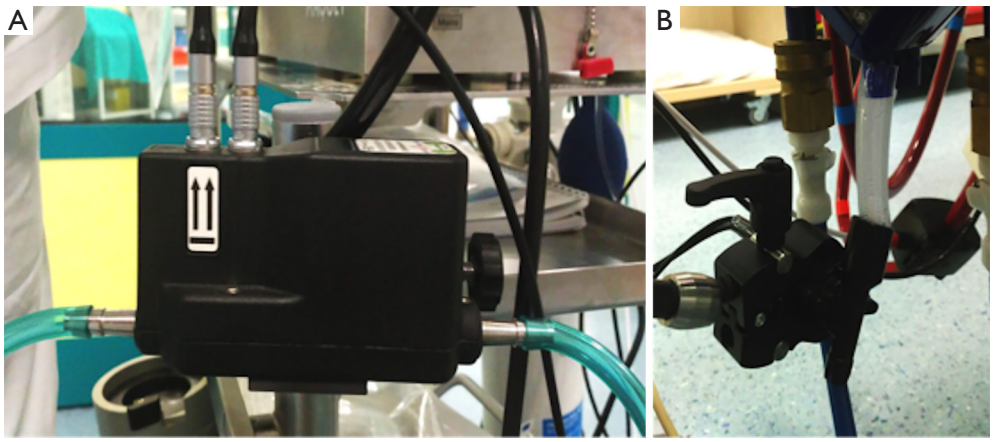

Figure 4 Gas measurement module (on the left, A) and exit CO_2 sensor (on the right, B) of a non-invasive diagnostic monitoring system, now being implemented in our clinical practise (System M4®, System Medical, Cheltenham, England, UK).

light between daily (or one-per-shift) analysis, in order to avoid dramatic and unforeseen changes, which would need to be dealt with in a well-timed manner.

The system we are using is focused on ML oxygenation function only. However, we are now introducing in our clinical practice a new non-invasive diagnostic monitoring system, with a gas measurement module (*Figure 4A*) and a gas outlet CO_2 sensor, which allows for continuous V'CO_2ML measurement (*Figure 4B*).

Monitoring both ML oxygenation and decarboxylation function could be helpful as these two sometimes do not fail at the same time. Moreover, analysis of both V'O_2ML and V'CO_2ML could be useful to estimate the NL gas exchange residual function in ML-NL interaction.

ML gas exchange monitoring in clinical practice

In a clinical case, we described how it was possible to monitor V'CO_2 partitioning between the NL and the ML, during ECMO weaning (22). It was useful to determine the progressive improvement of lung conditions, demonstrated by an increase of V'CO_2NL. It was possible at the same time to reduce ML GF, hence V'CO_2ML, and therefore finally removing the extracorporeal support.

The ML aging process could be defined as the progressive decay of ML gas transfer. V'O_2ML and V'CO_2ML have to be considered and checked separately as they may not always decay at the same time: ML performance could decrease because of the failure of one function, while the other is still more than efficient. It is possible to find different results in literature regarding the oxygenator half-life and its decay of efficacy. Lehle *et al.* observed a reduction in CO_2 elimination during the first 5 days of ECMO use, without any change in O_2 transfer (23). In a previous article, the same author described the requirement of ML replacements after a mean interval of 11±7 days in 3 out of 31 patients (10). In a retrospective study Lubnow *et al.* described ECMO substitution due to ML failure, between 6 and 12 days of use in 28 out of 83 patients (24), while Panigada *et al.*, in a total of 22 patients, with a median ECMO duration of 8 [6–13] days, observed the worsening of oxygenator performance in 7 (26%) patients (17).

Our group is carrying out pilot-studies founded on a new manner to evaluate ML functional decline, based on V'CO_2ML monitoring: every measured V'CO_2ML could be correlated to a testing workbench V'CO_2ML theoretic value, at the same GF/BF ratio, obtaining the so-called V'CO_2ML ratio (*Figure 5A*,*B*).

In a former preliminary abstract (25) we demonstrated a statistically significant decrease of ML measured/theoretical V'CO_2 ratio between the first and last day of use of 7 different MLs. We observed that mean V'CO_2ML ratio decreased from 0.97±0.17 to 0.75±0.17 (P=0.0121), while mean ML dead space (VdsML) increased from 0.24±0.07 to 0.47±0.09 (P=0.0005) (*Figure 6*). It could be explained by clot apposition on ML fibers, with the formation of ventilated but not perfused units, showed by the concurrent increase in VdsML (*Figure 7*). Even if further investigations are needed to confirm their value, CO_2 removal based indexes could represent useful additional early predictors of ML deterioration.

A monitoring system could be useful in daily clinical

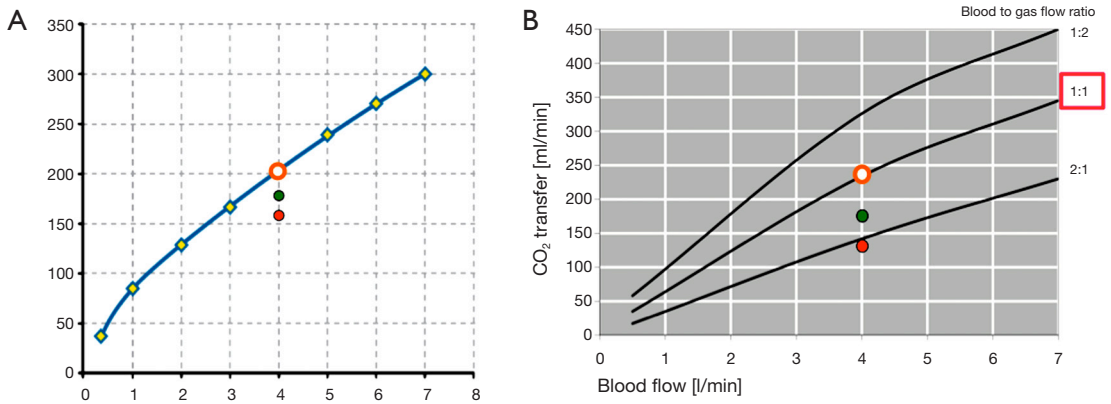

Figure 5 Factory data reporting V'CO_2ML bench reference values of ECMO Adult Long Term Oxygenator, EUROSETS (on the left, A)[#] and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany (on the right, B)[^]. Points represent an example of measured membrane lung (ML) CO_2 removal (V'CO_2ML) on first (green) and last (red) day of use, of two different MLs, in two different patients. For all the measurements we considered a blood flow (BF) of 4 L/min, with a blood flow/gas flow ratio (BF/GF) of 1 for both the MLs. We obtained the so-called V'CO_2ML ratio, dividing each value for the corresponding bench reference value, at the same BF (orange circle). [#], V'CO_2ML (ECMO Adult Long Term Oxygenator) data from EUROSETS S.r.l., Medolla, MO, Italy (modified figure, reproduction authorized by EUROSETS S.r.l). [^], V'CO_2ML (PLS-i Oxygenator) data from Maquet Cardiopulmonary GmbH Rastatt, Baden-Württemberg, Germany; Instructions for Use G-350, Version 01, 2016-05 (modified figure, reproduction authorized by Maquet Cardiopulmonary GmbH). ECMO, extracorporeal membrane oxygenation.

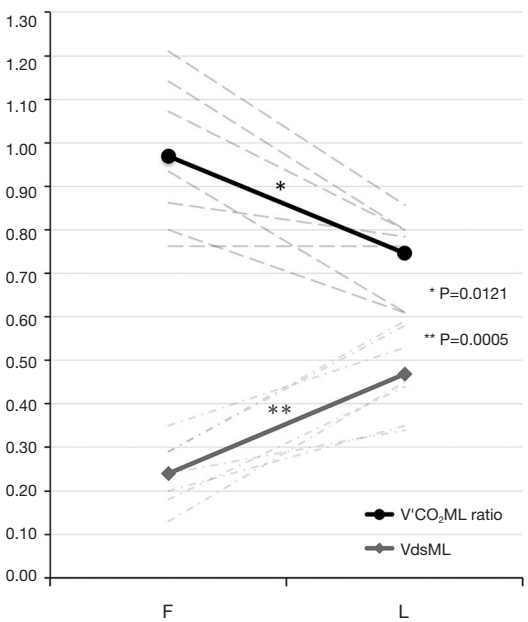

Figure 6 In a previous preliminary study[#] we considered the first (F) and last (L) day of use of 7 different oxygenators (ECMO Adult Long Term Oxygenator, EUROSETS and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany), for a mean duration of 11.57±4.69 days, used in 4 different adult ECMO patients (3 males, mean age 50±8 years). We correlated every measured membrane lung (ML) CO_2 removal (V'CO_2ML) value to a testing workbench V'CO_2ML theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called V'CO_2ML ratio. Interrupted lines represent each ML variations, while continuous lines indicate mean values changes, from F to L day of use. [#], Epis F, Pagani M, Biglia A, *et al.* Oxygenator performance assessment from CO_2 removal capacity during VV ECMO (abstract, poster, modified figure). 5th EuroELSO. June 2016, Glasgow, UK. ECMO, extracorporeal membrane oxygenation.

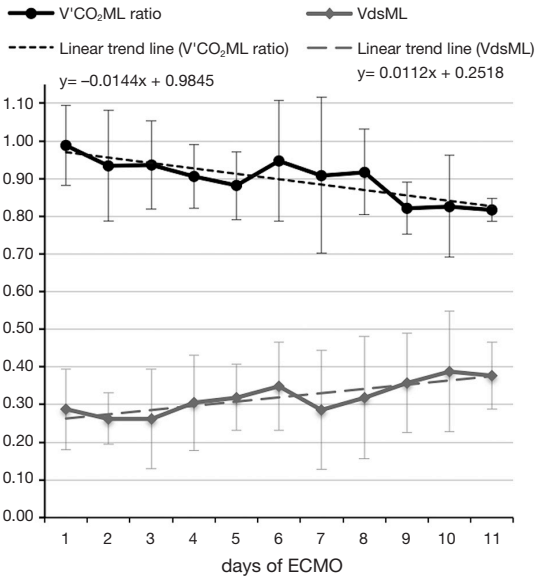

Figure 7 We considered daily collected data of 7 different oxygenators (ECMO Adult Long Term Oxygenator, EUROSETS and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany), used in 4 different adult ECMO patients (3 males, mean age 50±8 years), from a previous preliminary study[#]. We correlated every measured membrane lung (ML) CO_2 removal (V'CO_2ML) value to a testing workbench V'CO_2ML theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called V'CO_2ML ratio. We observed the decrease of mean V'CO_2ML ratio, which dropped from 0.94±0.15 to 0.80±0.13, and the concurrent rise of mean VdsML, from a value of 0.20±0.13 to 0.31±0.19. [#], Epis F, Pagani M, Biglia A, *et al*. Oxygenator performance assessment from CO_2 removal capacity during VV ECMO (abstract, poster). 5th EuroELSO. June 2016. Glasgow, UK.

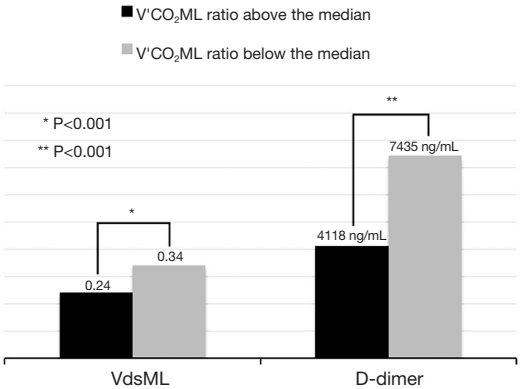

Figure 8 In a previous pilot-study[#] we considered a total of 16 oxygenators (ECMO Adult Long Term Oxygenator, EUROSETS and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany), used in 13 different adult patients (6 females, mean age 55±12 years). We correlated every measured membrane lung (ML) CO_2 removal (V'CO_2ML) value to a testing workbench V'CO_2ML theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called V'CO_2ML ratio. We divided V'CO_2ML ratio measurements in two different groups according to V'CO_2ML ratio median value (0.83, IQR 0.74–0.93). Measurements above the median were associated with inferior levels of ML dead space (VdsML) [0.24 (median, IQR 0.15–0.34) *vs.* 0.34 (median, IQR 0.24–0.43); P<0.001] and lower levels of D-dimer [4,118 ng/mL (median, IQR 1,996–7,412 ng/mL) *vs.* 7,435 ng/mL (median, IQR 4,968–10,654 ng/mL); P<0.001]. Comparisons of variables were made by Mann-Whitney test. [#], Epis F, Cremascoli L, Belliato M, *et al*. D-Dimer and CO_2 Removal Capacity: Another Way To Evaluate Oxygenator Performance During ECMO? Eur J Heart Fail 2017;19:59. Modified figure, reproduction authorized by John Wiley & Sons, Inc. IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

practice to evaluate oxygenator replacement timing by assessing ML efficiency, especially when it is running beyond its certification period. In a previous clinical case (21), we showed how V'O_2ML was useful to monitor oxygenator performance beyond the 15-day ML certification period, up to day 37.

A V'O_2ML acceptable for the metabolic demand of the patient has been maintained, with no substantial decline of ML performance, with an important contribution that might have come from a meticulous control of coagulation. Therefore, we underline the importance of laboratory monitoring, such as C-reactive protein, procalcitonin, haptoglobin, free blood Hb, D-dimer and coagulation tests, in order to get a perspective of inflammatory, haemolytic and thrombotic phenomena, triggered by the extracorporeal circuit.

D-dimer especially has been proposed as a good parameter of ML aging. It cannot be overlooked, as increased levels of plasma D-dimer could reveal clot apposition on ML fibers (26) and its deterioration (27). In another preliminary study, based on V'CO_2ML ratio, we have seen how the increased D-dimer levels could correlate significantly to decreased V'CO_2ML ratio and increased VdsML (28) (*Figure 8*). Therefore, these parameters might represent early predictors of ML performance decline, to guide ML replacement decision-making.

Rigorous and constant monitoring and check of ECMO systems with a proper management could then help to keep ML gas transfer power stable (29), even during long-run ECMO support.

Moreover, it is important to note that the ML aging process showed by monitoring data is not the only element

to make correct decisions about ML substitution and ECMO management. In fact, it is important to take into account the entire global clinical setting during extracorporeal assistance. Therefore, even if ML gas transfer deterioration could suggest an ongoing aging process, ML substitution could be postponed if it is sufficient for the patient's actual needs. It is fundamental to remember that the oxygenator change procedure is a life-threatening situation (30), also related to dangerous complications, such as hypoxia, heart rate alterations, cardiac arrest and embolic events. Then, if possible, a conservative attitude allows clinicians to protect the patient, globally reducing the cost of assistance.

Conclusions

Accurate ML gas transfer monitoring and simultaneous NL state evaluation represent an important adjunct in ECMO management, along with pressure drops measurement across the ECMO circuit and daily sampling for haemolysis and coagulation laboratory tests. They are all crucial to improve the safety of the technique with a more timely and precise analysis of ECMO performance, avoiding unforeseen abrupt ECMO failure. Additionally, an accurate analysis of NL status is fundamental to avoid complications both from ECMO and from the ventilator and to make decisions in the clinical setting, with a multi-dimensional approach.

In conclusion, ECMO real-time monitoring systems could allow a wide-ranging understanding of the complex patient-ECMO system and its appropriate clinical management. Further studies are necessary in order to improve and complete all the monitored parameters, increasing their accuracy and regulating their clinical use, in order to make them a gold standard for ECMO management.

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Footnote

Conflicts of Interest: M Belliato received fees as congress speaker and for consultancies from Eurosetes srl (Medolla, Italy), Maquet Cardiopulmonary GmbH (Rastatt, Baden-Württemberg, Germany), Hamilton Medical (Bonaduz, CH); F Epis has no conflicts of interest to declare.

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