

# Oxygenator performance and artificial-native lung interaction

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**Abstract:** During extracorporeal membrane oxygenation (ECMO), oxygen (O<sub>2</sub>) transfer (V'O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>) removal (V'CO<sub>2</sub>) 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<sub>2</sub> transfer (V'O<sub>2</sub>ML) is proportional to extracorporeal blood flow and the difference in O<sub>2</sub> content between each ML side, while ML CO<sub>2</sub> removal (V'CO<sub>2</sub>ML) can be calculated from ML gas flow and CO<sub>2</sub> 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<sub>2</sub>ML decay. Clot formation around fibers determines a ventilated but not perfused compartment, with a "dead space effect", negatively influencing V'CO<sub>2</sub>ML. 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 is 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<sub>2</sub>) transfer and carbon dioxide (CO<sub>2</sub>) 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<sub>2</sub> delivery

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

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

<sup>#</sup>, NL data from Chauhan S, Subin S. Extracorporeal membrane oxygenation, an anesthesiologist's perspective: physiology and principles. Part 1. *Ann Card Anaesth*. 2011 Sep-Dec;14(3):218-29. <sup>^</sup>, ML data from ECMO Adult Long Term Oxygenator Module Technical Characteristic (EUROSETS S.r.l., Medolla, MO, Italy).

and the total CO<sub>2</sub> 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,

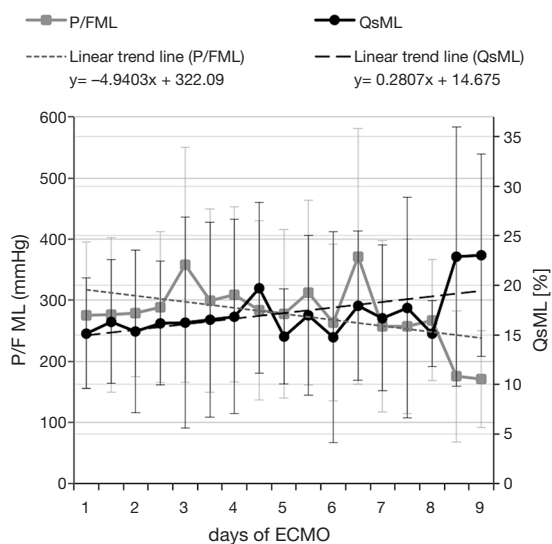
replacing patient pulmonary alveolar function, as its main functions are to transfer O<sub>2</sub> to the blood (V'O<sub>2</sub>ML) and to remove CO<sub>2</sub> (V'CO<sub>2</sub>ML).

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<sub>2</sub>ML to 350 mL/min compared to the NL O<sub>2</sub> transfer (V'O<sub>2</sub>NL), 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<sub>2</sub>ML (mL/min) is proportional to blood flow (BF, L/min) and the difference in O<sub>2</sub> 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  $15.15\% \pm 5.58\%$  to  $23.2\% \pm 10.20\%$ , and a contemporary decrease of P/FML, from a value of  $275.58 \pm 119.09$  to  $170.79 \pm 79.16$  mmHg. ECMO, extracorporeal membrane oxygenation.

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

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

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):

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

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

$$[(P_{ATM} - P_{H_2O}) \times F_iO_2ML - p_aCO_2/RQ]$$

as  $p_iO_2$ . In the previous formulas  $HbCO$  is Hb saturated in carbon monoxide,  $HbMet$  is methemoglobin,  $p_iO_2$  is oxygen partial pressure at ML gas inlet,  $P_{ATM}$  is atmospheric pressure,  $P_{H_2O}$  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<sub>2</sub> from patient's blood. The ML gas flow (GF) is the major determinant of ML CO<sub>2</sub> removal (V'CO<sub>2</sub>ML), which is relatively independent from BF (18). The increase of GF reduces the CO<sub>2</sub> partial pressure at ML sweep gas outlet (p<sub>e</sub>CO<sub>2</sub>), increasing the partial pressure gradient in between blood and gas phase and consequently augmenting V'CO<sub>2</sub>ML.

V'CO<sub>2</sub>ML (mL/min) can be easily calculated (19) from the ML GF (mL/min) and the CO<sub>2</sub> concentration at ML sweep gases outlet ([CO<sub>2</sub>]<sub>e</sub>, 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<sub>2</sub>ML power is directly proportional to GF, as in the NL CO<sub>2</sub> elimination (V'CO<sub>2</sub>NL), 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):

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

obtained from CO<sub>2</sub> partial pressure at the ML blood outlet (p<sub>post</sub>CO<sub>2</sub>, mmHg) and p<sub>e</sub>CO<sub>2</sub>, (mmHg), also measured with an infrared CO<sub>2</sub> analyser at sweep gas outlet.

Therefore, VdsML negatively influences V'CO<sub>2</sub>ML and it is compensated in clinical practice by a progressive increase of GF, in order to maintain a normal patient p<sub>a</sub>CO<sub>2</sub>.

### 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<sub>2</sub> content (C<sub>vmix</sub>O<sub>2</sub>), 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<sub>2</sub> (V'O<sub>2</sub>NL), 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<sub>a</sub>O<sub>2</sub> is afterwards the result of the total amount of O<sub>2</sub> transfer (V'O<sub>2</sub>), partitioned into V'O<sub>2</sub>ML and V'O<sub>2</sub>NL:

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

In a similar way, the total amount of CO<sub>2</sub> removal (V'CO<sub>2</sub>) from the patient's blood could be partitioned into V'CO<sub>2</sub>ML and V'CO<sub>2</sub>NL:

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

Once in the pulmonary capillaries, CO<sub>2</sub> readily diffuses to the alveolar space, passing through the alveolar-capillary membrane in an extremely efficient way, that CO<sub>2</sub> alveolar partial pressure (p<sub>A</sub>CO<sub>2</sub>) usually can be considered to be equal to that of the pulmonary end-capillary blood. Hence, p<sub>A</sub>CO<sub>2</sub> is the main important determinant of V'CO<sub>2</sub>NL. Alveolar ventilation is then fundamental to compensate the continuous CO<sub>2</sub> supplement to alveolar gas from pulmonary circulation, by reducing p<sub>A</sub>CO<sub>2</sub>.

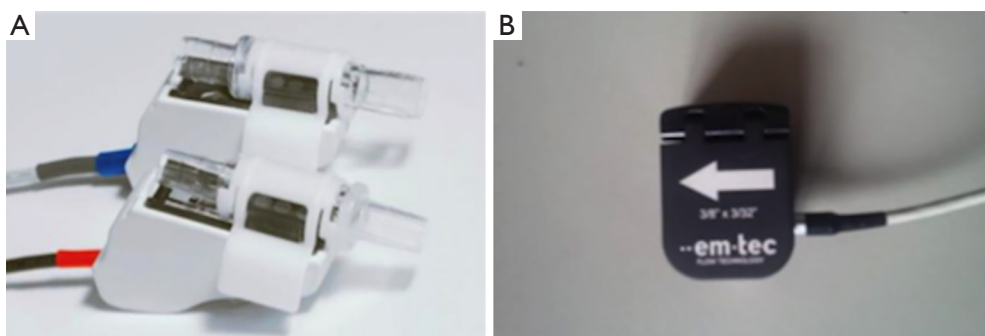
### NL and ML gas exchange monitoring

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<sub>2</sub> and V'CO<sub>2</sub> are shared differently, depends on ML and NL functional states and ECMO and mechanical ventilation settings.

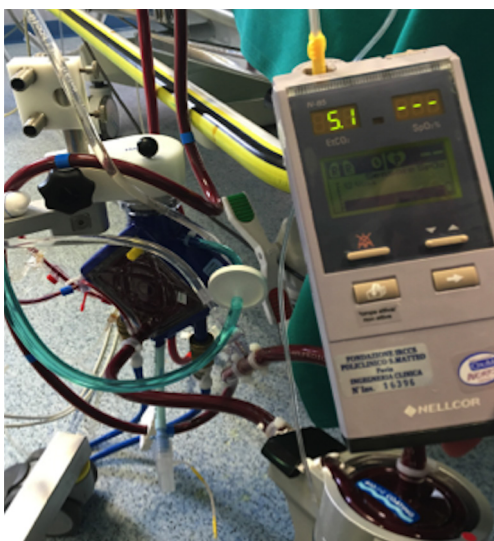
In order to evaluate all these data in their complexity, most centres use homemade electronic data sheets to collect raw data and calculate derived parameters of extreme importance, even though these informations are not continuous or calculated in real-time. Collecting these data can be cumbersome and 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<sub>s</sub>/Q<sub>BF</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> saturation (S<sub>v</sub>O<sub>2</sub>) and temperature (T<sub>ven</sub>) measurements. Probe B, denoted as the arterial probe, provides the

measurement of post-oxygenator (arterial) Hb O<sub>2</sub> saturation (S<sub>a</sub>O<sub>2</sub>) and temperature (T<sub>art</sub>). 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<sub>2</sub>ML maintains validity during VV ECMO. It is calculated according to the following simplified equation (21):

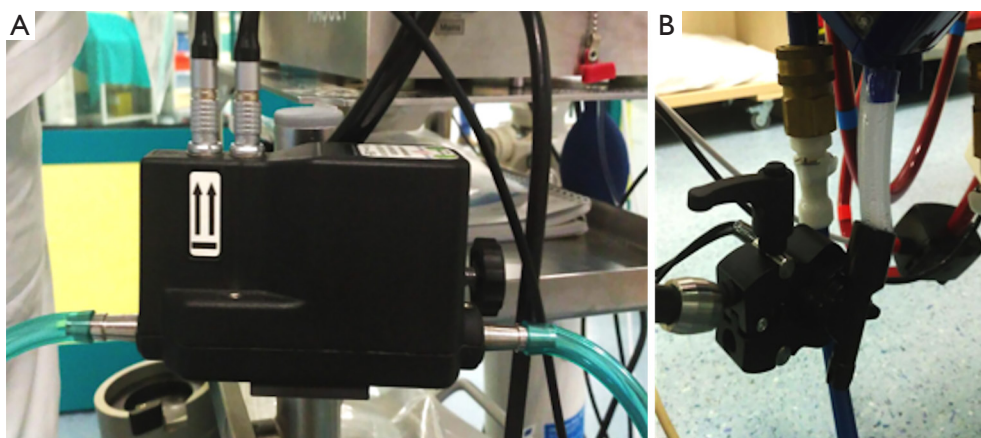
$$V'O_2ML = BF \times (k \times Hb \times S_aO_2 - k \times Hb \times S_vO_2)$$

using a coefficient ( $k = 13.8$ ), for V'O<sub>2</sub>ML expressed as mL/min, Hb as g/dl and BF as L/min.

The V'O<sub>2</sub>NL 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<sub>2</sub>NL is obtained by the volumetric capnometry function integrated into our mechanical ventilator. V'CO<sub>2</sub>ML is calculated at least on a daily basis by volumetric capnometry, applied to the ML, with an infrared CO<sub>2</sub> 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<sub>2</sub> sensor (on the right, B) of a non-invasive diagnostic monitoring system, now being implemented in our clinical practise (System M4<sup>®</sup>, 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<sub>2</sub> sensor, which allows for continuous V<sup>̇</sup>CO<sub>2</sub>ML 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<sup>̇</sup>O<sub>2</sub>ML and V<sup>̇</sup>CO<sub>2</sub>ML 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<sup>̇</sup>CO<sub>2</sub> 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<sup>̇</sup>CO<sub>2</sub>NL. It was possible at the same time to reduce ML GF, hence V<sup>̇</sup>CO<sub>2</sub>ML, and therefore finally removing the extracorporeal support.

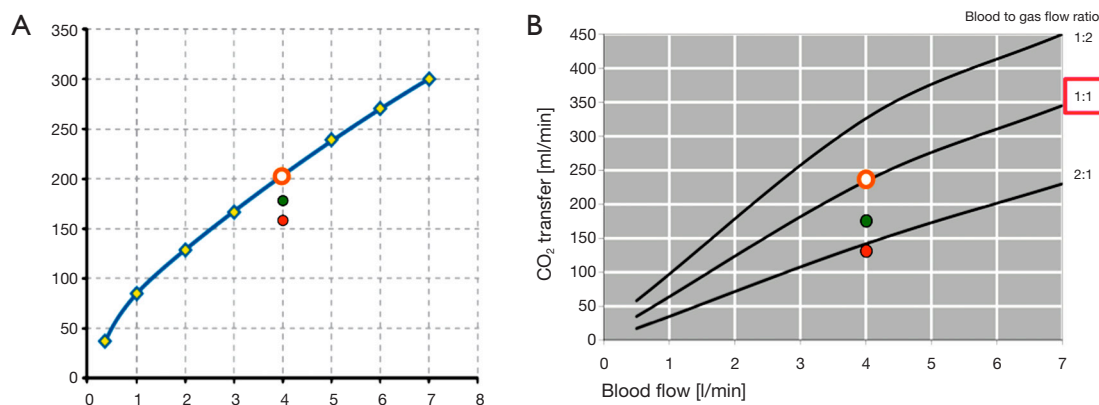
The ML aging process could be defined as the progressive decay of ML gas transfer. V<sup>̇</sup>O<sub>2</sub>ML and V<sup>̇</sup>CO<sub>2</sub>ML have to be considered and checked separately as they may not always decay at the same time: ML performance could decrease because of the failure of one function, 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<sub>2</sub> elimination during the first 5 days of ECMO use, without any change in O<sub>2</sub> 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).

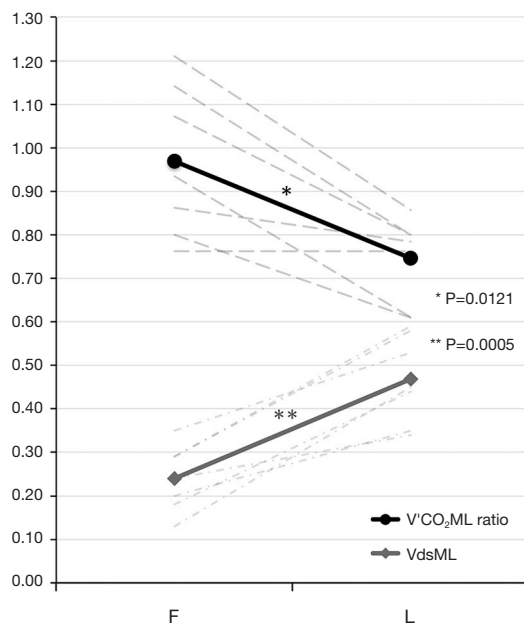
Our group is carrying out pilot-studies founded on a new manner to evaluate ML functional decline, based on V<sup>̇</sup>CO<sub>2</sub>ML monitoring: every measured V<sup>̇</sup>CO<sub>2</sub>ML could be correlated to a testing workbench V<sup>̇</sup>CO<sub>2</sub>ML theoretic value, at the same GF/BF ratio, obtaining the so-called V<sup>̇</sup>CO<sub>2</sub>ML ratio (Figure 5A,B).

In a former preliminary abstract (25) we demonstrated a statistically significant decrease of ML measured/theoretical V<sup>̇</sup>CO<sub>2</sub> ratio between the first and last day of use of 7 different MLs. We observed that mean V<sup>̇</sup>CO<sub>2</sub>ML ratio decreased from 0.97±0.17 to 0.75±0.17 (P=0.0121), while mean ML dead space (V<sub>ds</sub>ML) 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 V<sub>ds</sub>ML (Figure 7). Even if further investigations are needed to confirm their value, CO<sub>2</sub> removal based indexes could represent useful additional early predictors of ML deterioration.

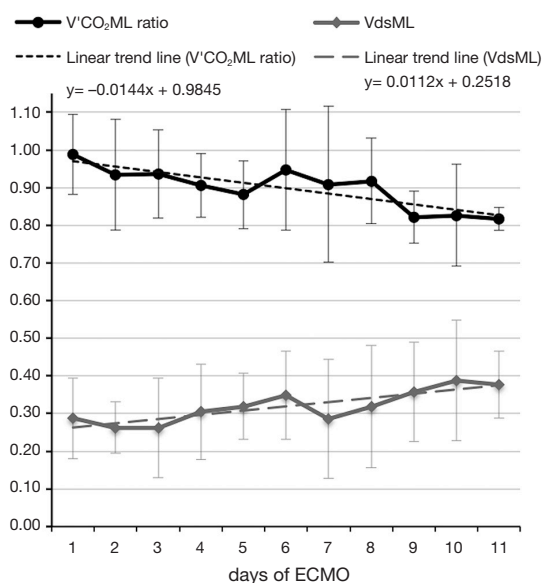
A monitoring system could be useful in daily clinical



**Figure 5** Factory data reporting  $V^{\text{CO}_2\text{ML}}$  bench reference values of ECMO Adult Long Term Oxygenator, EUROSETS (on the left, A)<sup>#</sup> and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany (on the right, B)<sup>^</sup>. Points represent an example of measured membrane lung (ML) CO<sub>2</sub> removal ( $V^{\text{CO}_2\text{ML}}$ ) 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  $V^{\text{CO}_2\text{ML}}$  ratio, dividing each value for the corresponding bench reference value, at the same BF (orange circle). <sup>#</sup>,  $V^{\text{CO}_2\text{ML}}$  (ECMO Adult Long Term Oxygenator) data from EUROSETS S.r.l., Medolla, MO, Italy (modified figure, reproduction authorized by EUROSETS S.r.l.). <sup>^</sup>,  $V^{\text{CO}_2\text{ML}}$  (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).



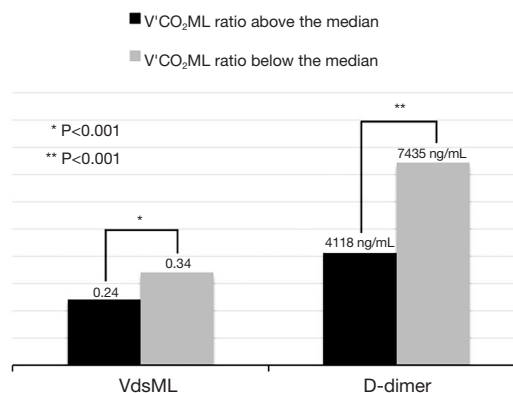
**Figure 6** In a previous preliminary study<sup>#</sup> we considered the first (F) and last (L) day of use of 7 different oxygenators (ECMO Adult Long Term Oxygenator, EUROSETS and PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany), for a mean duration of  $11.57 \pm 4.69$  days, used in 4 different adult ECMO patients (3 males, mean age  $50 \pm 8$  years). We correlated every measured membrane lung (ML) CO<sub>2</sub> removal ( $V^{\text{CO}_2\text{ML}}$ ) value to a testing workbench  $V^{\text{CO}_2\text{ML}}$  theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called  $V^{\text{CO}_2\text{ML}}$  ratio. Interrupted lines represent each ML variations, while continuous lines indicate mean values changes, from F to L day of use. <sup>#</sup>, Epis F, Pagani M, Biglia A, et al. Oxygenator performance assessment from CO<sub>2</sub> removal capacity during vvECMO (abstract, poster, modified figure). 5th EuroELSO. June 2016, Glasgow, UK.



**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  $50 \pm 8$  years), from a previous preliminary study<sup>#</sup>. We correlated every measured membrane lung (ML) CO<sub>2</sub> removal (V'CO<sub>2</sub>/ML) value to a testing workbench V'CO<sub>2</sub>/ML theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called V'CO<sub>2</sub>/ML ratio. We observed the decrease of mean V'CO<sub>2</sub>/ML ratio, which dropped from  $0.94 \pm 0.15$  to  $0.80 \pm 0.13$ , and the concurrent rise of mean VdsML, from a value of  $0.20 \pm 0.13$  to  $0.31 \pm 0.19$ .<sup>#</sup>, Epis F, Pagni M, Biglia A, *et al.* Oxygenator performance assessment from CO<sub>2</sub> removal capacity during vvECMO (abstract, poster). 5th EuroELSO. June 2016. Glasgow, UK.

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<sub>2</sub>/ML was useful to monitor oxygenator performance beyond the 15-day ML certification period, up to day 37.

A V'O<sub>2</sub>/ML 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.



**Figure 8** In a previous pilot-study<sup>#</sup> 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  $55 \pm 12$  years). We correlated every measured membrane lung (ML) CO<sub>2</sub> removal (V'CO<sub>2</sub>/ML) value to a testing workbench V'CO<sub>2</sub>/ML theoretic value, at the same gas flow/blood flow ratio (GF/BF), obtaining the so-called V'CO<sub>2</sub>/ML ratio. We divided V'CO<sub>2</sub>/ML ratio measurements in two different groups according to V'CO<sub>2</sub>/ML 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 1996–7412 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.<sup>#</sup>, Epis F, Cremascoli L, Belliato M, *et al.* D-Dimer and CO<sub>2</sub> Removal Capacity: Another Way To Evaluate Oxygenator Performance During ECMO? *Eur J Heart Fail.* 2017 May;19(2):59. modified figure, reproduction authorized by John Wiley & Sons, Inc.

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<sub>2</sub>/ML ratio, we have seen how the increased D-dimer levels could correlate significantly to decreased V'CO<sub>2</sub>/ML 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

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