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ORIGINAL ARTICLE

**Artificial Lung / ECMO**

# Effects on membrane lung gas exchange of an intermittent high gas flow recruitment maneuver: preliminary data in veno-venous ECMO patients

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**Abstract** Gas exchange capabilities of polymethylpentene membrane lungs (MLs) worsen over time. ML deterioration is related to protein deposit and clot formation. Condensation and trapping of water vapor inside ML hollow fibers might affect ML performances as well. Increasing sweep gas flow (GF) could remove such fluid. The purpose of this study was to evaluate the effects on ML gas exchange of a recruitment maneuver (RM) based on a brief increase in GF, during veno-venous ECMO support. Short-term (15 min) effects of 20 RMs were assessed. RM raised ML $CO_2$ removal from 149 ± 37 to 174 ± 41 ml/min ($p < 0.001$). Conversely, RM did not improve ML $O_2$ transfer (155 ± 31 and 158 ± 31 ml/min before and after RM, respectively). ML outlet $pCO_2$ decreased after RM from 51.2 ± 5.8 to 45.8 ± 5.4 mmHg ($p < 0.001$), while ML outlet $pO_2$ increased from 520 ± 61 to 555 ± 51 mmHg ($p < 0.001$). Both ML dead space and shunt fractions decreased from 47.8 ± 15.3 to 29.6 ± 14.7 % ($p < 0.001$) and from 8.8 ± 4.2 to 7.0 ± 3.8 % ($p < 0.001$), respectively. Furthermore, a subset of 5 RMs was evaluated on a 6-h time frame. The beneficial effects on ML performances due to the RM gradually diminished and waned over a 6-h interval after the RM. The RM improved ML $CO_2$ removal substantially, albeit temporarily. ML oxygenation performance was marginally affected.

**Keywords** Extracorporeal membrane oxygenation · Oxygenators · Respiratory dead space · Water loss · Insensible

## Introduction

The use of extracorporeal membrane oxygenation (ECMO) for the management of the most severe cases of acute respiratory failure is becoming increasingly widespread, thanks also to technological advances [1, 2]. The development of polymethylpentene (PMP) hollow fiber membrane lung oxygenator (membrane lung, ML) was likely the most important technical improvement in this field. Indeed, its small priming volume, little resistance to blood flow and lack of plasma leakage make it particularly fit for long-term treatment [3]. Notwithstanding, the gas exchange performances of PMP ML worsen over time, and prompt substitution of the oxygenator is required when it fails to support metabolic needs of the patient [4]. The deterioration of ML performance has been related to protein deposit and clot formation on ML surfaces in contact with blood [5, 6]. Moreover, some in vitro tests showed considerable water losses from PMP MLs [7, 8]. In non-porous PMP MLs, plasmatic water dissolves into the surface of the membrane and migrates along its concentration gradient, followed by desorption and evaporation on the

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gas side [9, 10]. Following condensation, a fraction of this liquid is trapped inside the hollow fiber lumen, worsening ML gas exchange capability. Extracorporeal Life Support Organization (ELSO) guidelines suggest that the water vapor condensed inside the ML could be cleared by intermittently increasing sweep gas flow (GF) [11]. In clinical practice, we are used to perform occasionally this type of maneuvers, in order to improve ML gas transfer performance. However, to the best of our knowledge, effects of intermittently increasing sweep GF on gas exchange capabilities of a ML have not been reported yet.

Primary aim of this study was to evaluate the effects of the application of a "recruitment maneuver" (RM) based on a brief increase in GF on the gas exchange performances of PMP MLs, in patients connected to veno-venous ECMO support.

## Materials and methods

The study protocol was approved by the local ethics committee (San Gerardo Hospital, Monza, Italy). Twenty RMs were evaluated, performed in 7 adult patients (4 males and 3 females, age 47 ± 14) admitted to the intensive care unit of San Gerardo Hospital from January 2014 to July 2014, and treated with veno-venous ECMO. The RMs were applied in 13 MLs: Nine MLs were studied once, three MLs twice, while one ML underwent the RM five times. The studied RMs were not performed more than once a day.

All patients were connected to the PLS system (Maquet, Getinge Group, Goteborg, Sweden), composed of a centrifugal pump (Rotaflow Centrifugal Pump, Maquet) and an adult PMP ML (PLS-i Oxygenator, Maquet). In the extracorporeal circuit, two ports were integrated at the blood inlet and blood outlet of the ML (i.e., Blood_IN and Blood_OUT, respectively) in order to measure circuit pressures and withdraw blood samples. Moreover, a port was incorporated at the inlet of the ML sweep gases (Gas_IN) for pressure monitoring, while a port was present at the outlet of the ML sweep gases (Gas_OUT) to measure $CO_2$ concentration. The RM consisted in a 30-s increase in GF above the 10 l/min notch of the flow meter scale (Flowmeter 3500 CP-G, Sechrist, Anaheim, CA), until pressure at the Gas_IN port ranged between 25 and 30 mmHg. In a preliminary in vitro test, this pressure level corresponded to a GF around 25 l/min. At variance, standardizing the RM according to a high sweep GF would have not been an easy task to perform at the bedside in the absence of a pneumotachograph, since the maximum notch of our flow meter scale was just 10 l/min. We decided the RM to last 30 s, since in preliminary clinical tests, we observed water pouring from the Gas_OUT to stop after such time period.

To evaluate the short-term effects of the RM, two chronological steps were carried out before (i.e., Baseline step) and 15 min after the application of the RM (i.e., After-RM step). Ventilator settings, centrifugal pump revolutions per minutes (RPM) and GF level were set by the caregiver and were not changed between steps. The ML inspiratory oxygen fraction ($FiO_2ML$) was set at 100 %, since in our clinical practice, we are used to perform ML gas exchange evaluation at this $FiO_2ML$ level. Moreover, at Baseline and After-RM steps, hemodynamic parameters, ECMO blood flow (BF), pressures at Blood_IN and Blood_OUT were recorded. Furthermore, at both time points, blood was sampled from Blood_IN and Blood_OUT ports for blood gas analyses (COBAS B 221, Roche, Basel, Switzerland). Finally, $CO_2$ concentration (parts per million) was measured at Gas_OUT with an infrared $CO_2$ analyzer (WMA-4; GMR Strumenti SAS, Firenze, Italy).

To assess the long-term effects of the RM, a subset of 5 RMs were studied also on a 6-h time frame. The aforementioned parameters were collected 1, 2, 4 and 6 h after the RM (1-h RM step, 2-h RM step, 4-h RM step and 6-h RM step, respectively). Centrifugal pump RPM and GF were kept constant during this 6-h evaluation. $FiO_2ML$ was set at 100 % during data and samples collections.

For each step, the ML oxygen transfer ($VO_2$, ml/min) was computed according Fick equation. Moreover, mixed $CO_2$ partial pressure measured at the ML gas outlet ($peCO_2$, mmHg) and ML $CO_2$ removal ($VCO_2$, ml/min) were calculated as previously described by Zanella et al. [12]. The ML $CO_2$ removal efficiency was computed as the ratio between $VCO_2$ and the total $CO_2$ content in Blood_IN [13]. Furthermore, the Riley's three-compartment model was utilized to compute the ML shunt ($Q_s/Q_t$, %) and the ML dead space ($V_d/V_t$, %) fractions during each step [14]. According to Riley's model, a ML may be envisaged as made up of three ideal compartments: one having ideal ventilation–perfusion ratio, one being perfused but not ventilated (i.e., shunt), and one being ventilated but not perfused (i.e., dead space). Following this model, shunt and dead space are, respectively, accountable for the reduction in oxygen transfer and carbon dioxide removal of a ML. Finally, we computed the ML resistance to BF (mmHg/l/min). A detailed description of these equations is provided in the Online Supplement.

Data are presented as mean ± standard deviations (SD) or median and interquartile range (IQR), when appropriate. A generalized linear mixed model with patients and items MLs as random effects was utilized to evaluate the effects of the RM and time. Tukey test was used for post hoc multiple comparisons. Correlation analyses were carried out via the Pearson correlation method. $R^2$ was then calculated to show eventual goodness of fit. A $p$ value below 0.05 was considered statistically significant. Statistical analysis was performed using the JMP 11 statistical software (SAS, Cary, NC, USA).

## Results

ECMO parameters, ventilator settings and arterial blood gas analyses at study entry are summarized in Table 1. The median number of days after commencement of ECMO was 11.5 (IQR 4.5–35.5), while the median number of MLs days of use was 4.0 (IQR 2.0–8.0).

The RM raised $VCO_2$ from 149 ± 37 to 174 ± 41 ml/min (Fig. 1, Panel A) ($p < 0.001$). Similarly, the RM increased the ML $CO_2$ removal efficiency from 5.8 ± 1.4 to 7.1 ± 1.5 % ($p < 0.001$). Subsequent to the RM, $peCO_2$ increased from 21.3 ± 0.6 to 24.9 ± 0.6 mmHg ($p < 0.001$). Conversely, RM did not improve $VO_2$ (155 ± 31 vs. 158 ± 31 ml/min, Baseline and After-RM, respectively) (Fig. 1, Panel B).

Table 2 reports the blood gas analyses of circuit samples. Subsequent to the RM, pH of both Blood_IN and Blood_OUT samples increased, and $pCO_2$ and bicarbonate of both Blood_IN and Blood_OUT samples decreased. Subsequent to the RM, $pO_2$ of Blood_IN sample reduced, while $pO_2$ of Blood_OUT sample increased. No effects of the RM on oxygen hemoglobin saturation of both Blood_IN and Blood_OUT samples were detected.

**Table 1** ECMO parameters, ventilator settings and arterial blood gas analyses at study entry

| ECMO parameters | |
|---|---|
| Centrifugal pump Revolutions per minutes (RPM) | 2529 ± 269 |
| Blood flow (l/min) | 3.5 ± 0.5 |
| Gas flow (l/min) | 5 ± 2 |
| $FiO_2ML$ (%) | 82 ± 22 |
| **Ventilation Settings** | |
| Inspired oxygen fraction (%) | 42 ± 13 |
| PEEP pressure ($cmH_2O$) | 11 ± 5 |
| Mean airway pressure ($cmH_2O$) | 16 ± 4 |
| Plateau pressure ($cmH_2O$) | 25 ± 4 |
| Tidal volume (ml/kg) | 3.7 ± 1.1 |
| Minute volume (l/min) | 2.9 ± 1.2 |
| Compliance ($ml/cmH_2O$) | 20.0 ± 8.9 |
| **Arterial blood gas analyses** | |
| pH | 7.423 ± 0.032 |
| $pCO_2$ (mmHg) | 47.8 ± 4.7 |
| $pO_2$ (mmHg) | 83.7 ± 13.7 |
| $HbO_2$ (%) | 95.9 ± 1.7 |
| Hemoglobin (g/dl) | 11.2 ± 0.7 |

Data are reported as mean ± standard deviations

The RM reduced $V_d/V_t$ from 47.8 ± 15.3 to 29.6 ± 14.7 % ($p < 0.001$) (Fig. 2, Panel A). Application of the RM was always associated with a reduction in $V_d/V_t$. The RM reduced $Q_s/Q_t$ from 8.8 ± 4.2 to 7.0 ± 3.8 % ($p < 0.001$) (Fig. 2, Panel B). Noticeably, three RMs were not associated with a beneficial effect on $Q_s/Q_t$ (for gas exchange data of each RM see Table S1, Online supplement).

We subdivided the 20 RMs in two groups according to $V_d/V_t$ improvement and lifespan of the ML at the moment of RM application. The RMs applied in MLs between the second and ninth day of use showed a much greater $V_d/V_t$ reduction than the RMs applied in MLs at first day of use or in MLs older than 9 days (21.8 ± 6.8 and 3.5 ± 1.5 %, respectively, $p < 0.001$). On the contrary, no difference in $Q_s/Q_t$ reduction was registered between these two groups (1.6 ± 1.6 and 2.5 ± 1.5 %, first and second group, respectively).

$V_d/V_t$ measured at Baseline step correlated with ML days of use ($r^2 = 0.276$ and $p < 0.05$) (Figure S1, Online supplement, Panel A). Moreover, a stronger correlation was detected between $V_d/V_t$ measured after the RM and ML day of use ($r^2 = 0.541$ and $p < 0.001$) (Figure S1, online supplement, Panel B). Measurements of $Q_s/Q_t$ obtained before and after the RM correlated with ML days of use as well ($r^2 = 0.350$, $p < 0.05$ and $r^2 = 0.283$, $p < 0.05$, Baseline step and After-RM step, respectively) (see online supplement, Figure S2). Moreover, at Baseline step, $V_d/V_t$ did not correlate with the corresponding $Q_s/Q_t$ ($r^2 = 0.142$) (see online supplement, Figure S3, Panel A), whereas a good correlation was detected between the measurement of $V_d/V_t$ and $Q_s/Q_t$ obtained after the RM ($r^2 = 0.456$ and $p < 0.05$) (see Online supplement, Figure S3, Panel B).

No statistically significant differences between Baseline and After-RM measurements of BF (3.49 ± 0.53 and 3.53 ± 0.53 l/min, respectively), Blood_in-ML pressure (115 ± 20 and 117 ± 21 mmHg, respectively) and Blood_out-ML pressure (91 ± 17 and 93 ± 20 mmHg, respectively) were observed. As a result, RM did not change ML resistance (6.97 ± 1.75 and 6.87 ± 1.71 mmHg/l/min, Baseline and After-RM, respectively). During RMs, Blood_OUT pressure was always higher than the gas pressure at the Gas_IN (i.e., 30 mmHg). During all RMs, fluid poured from Gas_OUT port. Moreover, hemodynamics did not vary between Baseline step and After-RM step (see Online supplement, Table S2).

During the 6-h evaluation of the five RMs, GF and pump RPM were kept constant (6 ± 1 and 2458 ± 102 l/min, respectively) and BF was 3.5 ± 0.3 l/min.

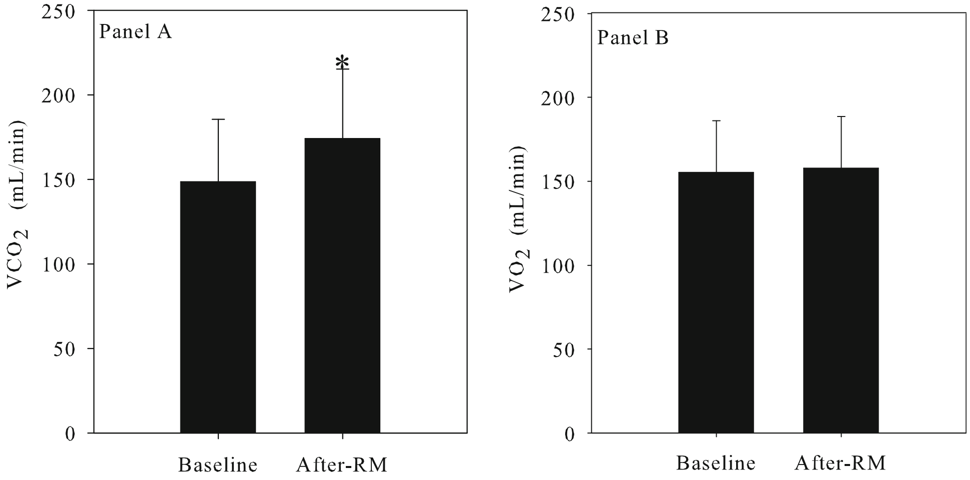

**Fig. 1** Effects of the recruitment maneuver on membrane lung (ML) performances. *Panel A*: ML carbon dioxide removal ($V\text{CO}_2$, ml/min) at Baseline and After-RM steps. *Panel B*: ML oxygen transfer ($V\text{O}_2$, ml/min) at Baseline and After-RM steps. Data are represented as mean ± standard deviation, $^*p < 0.001$ vs Baseline step

**Table 2** Circuitry blood gas analyses at Baseline and After-RM steps

| | Baseline | After-RM | *p* value |
|---|---|---|---|
| Blood_IN | | | |
| pH | 7.411 ± 0.033 | 7.441 ± 0.037 | <0.001 |
| $p\text{CO}_2$ (mmHg) | 51.2 ± 5.8 | 45.8 ± 5.4 | <0.001 |
| $\text{HCO}_3^-$ (mMol/l) | 31.7 ± 3.7 | 30.5 ± 3.4 | <0.05 |
| $p\text{O}_2$ (mmHg) | 45.6 ± 4.4 | 43.8 ± 4.3 | <0.05 |
| $\text{HbO}_2$ (%) | 78.4 ± 4.4 | 78.6 ± 4.7 | 0.65 |
| Blood_OUT | | | |
| pH | 7.472 ± 0.029 | 7.518 ± 0.037 | <0.001 |
| $p\text{CO}_2$ (mmHg) | 40.9 ± 4.8 | 35.4 ± 4.3 | <0.001 |
| $\text{HCO}_3^-$ (mMol/l) | 29.2 ± 3.5 | 28.1 ± 3.3 | <0.001 |
| $p\text{O}_2$ (mmHg) | 520.2 ± 60.6 | 554.9 ± 51.2 | <0.001 |
| $\text{HbO}_2$ (%) | 97.7 ± 0.3 | 97.7 ± 0.3 | 0.83 |

Blood_IN and Blood_OUT are the blood withdrawals before and after the ML, respectively. Data are reported as mean ± standard deviations

Figure 3 represents changes over time of $V_d/V_t$ and $Q_s/Q_t$ subsequent to the RM. The long-term study confirmed the capability of RM in reducing $V_d/V_t$ and $Q_s/Q_t$. The beneficial effects on $V_d/V_t$ and $Q_s/Q_t$ gradually diminished during the hours following the RM, to the point of being completely voided after 6 h (for the measurements of $V\text{CO}_2$, $V\text{O}_2$ and circuitry blood gas analyses during long-term RM evaluation, see Online supplement, Table S3).

## Discussion

The primary objective of this study was to evaluate the effects on ML gas exchange of a ML recruitment maneuver consisting in a brief increase in sweep GF. RM improved ML carbon dioxide extraction, albeit temporarily. Contrarily, effects of the RM on oxygen delivery by the ML were marginal.

ELSO guidelines suggest that temporary raising ML gas flow may be utilized to eliminate water vapor condense [11]. Clinical experience suggests fluid trapping inside ML hollow fibers to be associated with deterioration of ML $\text{CO}_2$ removal performances [15]. However, to the best of our knowledge, no evidence on the effects on ML gas exchange of intermittent high gas flow maneuvers has been reported yet, especially in PMP MLs.

We observed that a RM consisting of a temporary manipulation of sweep gas flow raised $V\text{CO}_2$ by a noteworthy 17 %. Therefore, subsequent to the RM, ML $\text{CO}_2$ removal efficiency ratio substantially increased (i.e., 23 %). Contrarily, $V\text{O}_2$ was not affected by the RM. Indeed, $p\text{O}_2$ of Blood_OUT increased by 35 mmHg, but this did not result in a higher $V\text{O}_2$ since hemoglobin of Blood_OUT was completely saturated even before the RM. During the RM, no adverse effects were observed, as regards to hemodynamics, ventilation and mechanical impairments of the device. Moreover, at least in this study's setting, we may exclude the possibility of gas embolism, since Gas_IN pressure during RM was always much lower than the corresponding blood circuit one.

The application of the RM was associated with a reduction in $Q_s/Q_t$ and $V_d/V_t$. We observed $Q_s/Q_t$ before the RM averaged 9 %, with the highest value reaching 23 %. Therefore, we confirm previous studies during which, in short-term applications (i.e., cardiopulmonary bypass surgery), $Q_s/Q_t$ of polypropylene ML ranged between 5 and 25 % [16, 17]. At variance, we do not have the knowledge of previous reports regarding ML $V_d/V_t$. $V_d/V_t$ was negligible in brand-new MLs, but rose over 40 % after the first day of use. The RM was capable of correcting a considerable fraction of this $V_d/V_t$, suggesting $V_d/V_t$ not to be subsequent to protein and clot deposits solely [6]. Since during RM we observed liquid to be released from the gas outlet, we may argue that fluid entrapment inside the hollow fibers may affect ML gas exchange capabilities.

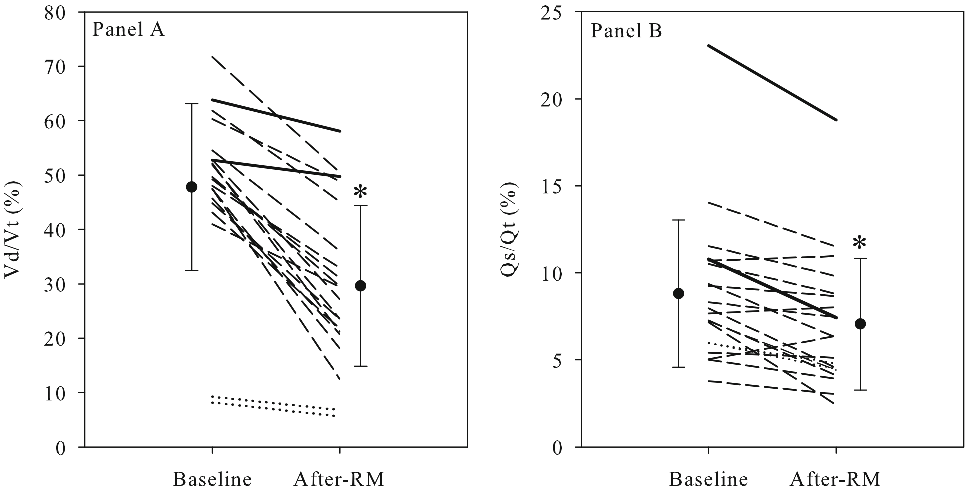

**Fig. 2** Effect of the recruitment maneuver on membrane lung (ML) dead space and shunt. *Panel A*: ML dead space fraction ($V_d/V_t$, %) at Baseline and After-RM steps. *Panel B*: ML shunt fraction ($Q_s/Q_t$, %) at Baseline and After-RM steps. *Thin dotted lines* represent MLs tested at the first day of use, while *thick dotted lines* indicate MLs tested between second and ninth day of use and *continuous lines* show MLs over ninth day of use. $V_d/V_t$ and $Q_s/Q_t$ (*Panel A* and *Panel B*, respectively) are also reported as mean ± standard deviations at Baseline and After-RM steps, * $p < 0.001$ vs Baseline step

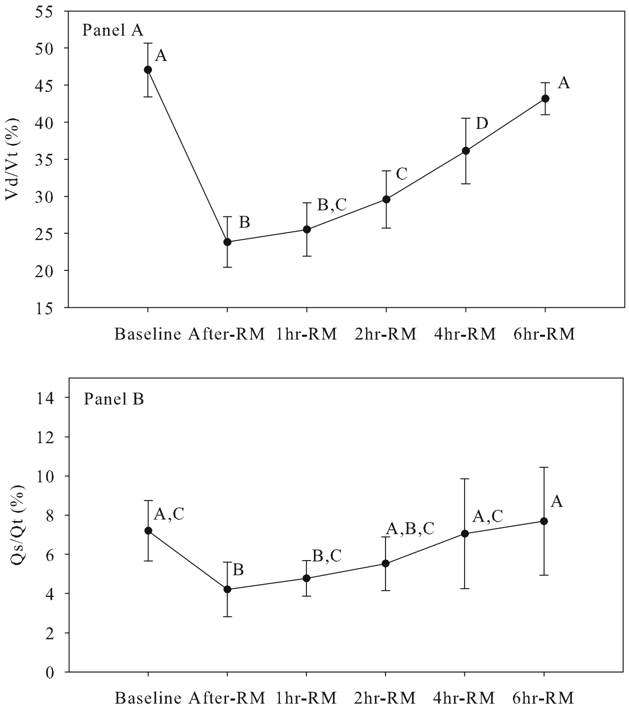

**Fig. 3** Effects of the recruitment maneuver during the 6-h evaluation. *Panel A*: membrane lung (ML) dead space fraction ($V_d/V_t$, %). *Panel B*: ML shunt fraction ($Q_s/Q_t$, %). In both panels, horizontal axis represents time steps. Data are represented as mean ± standard deviations. Steps not connected by the same letter are significantly different ($p < 0.05$)

Nevertheless, we could not exclude that the beneficial effects of the RM may be due to other causes (e.g., collapsed hollow fiber re-expansion). Assessing the reasons why RM is associated with an improvement in $CO_2$ removal rather than oxygenation goes beyond the scopes of this study. However, we may hypothesize that water trapping raises preferentially the resistance to gas flow of well-perfused ML regions, driving sweep gases toward less or non-perfused ML regions and thus increasing dead space fraction of the ML.

Albeit our study was not planned or designed to evaluate specifically the effects of the ML lifespan on ML performances and the response to the RM, we detected interesting correlations. The effects of the RM on $V_d/V_t$ were stronger in MLs employed for less than 9 days. Arguably, in older MLs, the $V_d/V_t$ could be mostly related to clot formation on the blood side of the ML, rather than to other reversible factors. We observed $Q_s/Q_t$ and $V_d/V_t$ to be associated with the day of use of the ML, both at Baseline and After-RM steps. Interestingly, the correlation between After-RM $V_d/V_t$ and ML days of use was stronger than between Baseline $V_d/V_t$ and ML days of use. This might suggest that the $V_d/V_t$ measurement obtained after the RM could better relate to ML impairment due to clotting. Furthermore, $V_d/V_t$ was correlated with $Q_s/Q_t$ after the RM, while no association was detected for these variables when measured before RM. This may suggest that, after correction of the reversible quote of $V_d/V_t$ and $Q_s/Q_t$ by the RM, the remaining fraction of both these defects worsens concurrently over time, albeit in different amounts.

As observed by our long-term evaluation, effects of RM on $V_d/V_t$ and $Q_s/Q_t$ were transient. Indeed, just after few hours of the RM, they returned to basal levels. Thus, the RM could be repeated cyclically to maintain the best gas exchange performances, by means of an automatic RM device applied to gas flow meter of the ML.

The potential clinical applications of a ML RM like this are various. An intermittent high gas flow maneuver should always be performed before daily ML gas exchange evaluation, to better assess the effective deterioration of the ML performance due to clotting impairment. Furthermore, in critically ill patients, substitution of circuitry is a high-risk procedure [18]. Particularly, in patients totally depending on ECMO support, emergency exchange of the ML might turn into a catastrophe if performed by inadequately staffed personnel. Consequently, having the possibility to improve and lengthen ML performances, even for few hours, may be important in the daily clinical practice. Moreover, the RM may be utilized to reduce medical gas consumption. This could be useful in circumstances where supplies of medical gases are limited (i.e., out of hospital ECMO transfer) [19]. Furthermore, RM might be utilized for $CO_2$ removal system ($ECCO_2R$) as well. Indeed, an in vitro study showed that ML water losses were not related to ML exchange surface or BF, but just to the sweep gas flow [20]. Therefore, in $ECCO_2R$ systems, water losses could be the same or greater than during full ECMO support. Notably, the Hemolung device (Alung, Alung Technologies, Pittsburgh, PA) is a peculiar $ECCO_2R$ apparatus whose sweep gases are supplied under negative pressure [21]. This device cyclically (i.e., every 15 min) applies a more negative GF pressure (i.e., purge cycle) to remove residual moisture trapped inside ML fibers. Although the RM hereby described acts with a positive GF pressure, it has the same rationale of the Hemolung purge cycle.

Some limitations of the present study deserve to be discussed. Biases may originate from the use of a specific PMP ML. However, commercially available MLs are based on similar hollow fiber technology; thus, we believe that the results comparable with ours could be achieved regardless of the ML model used. Limitations may come from the design of this preliminary study. Indeed, calculation of $V_d/V_t$ was not standardized for a given GF level, since it was maintained as set by the physician. However, GF level was kept constant during all the study phases, except during the RM. Moreover, GF level values before and after RM were set and recorded by means of flow meter without further GF measurements (i.e., pneumotachograph). However, since the accuracy of this model of flow meter is about 3 %, the error in GF setting and measurements might be considered minimal. Biases may derive from the RM setting (i.e., duration and pressure level). It is possible that different RM settings (i.e., duration, GF pressure level, sweep GF) could influence the effects of the RM as regards to ML gas exchange. Similarly, by study design, ML lifespan, blood flow and gas flow were not evaluated prospectively. Further controlled studies will be necessary to validate our results.

## Conclusion

This study shows that a RM consisting in a brief increase in GF is an effective procedure to improve ML carbon dioxide extraction (i.e., +17 %) by means of reduction of the dead space associated with water accumulation inside ML hollow fibers. Such beneficial effects are transient; thus, development of an automatic device capable of cyclical RM may be of use. Further studies are warranted to evaluate if the application of the RM on a systematic time frame could provide clinically meaningful outcomes.

**Conflict of interest** The authors declare that they have no conflict of interest.

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