

Limitations of arterial partial pressure of oxygen to fraction of inspired oxygen ratio for the evaluation of donor lung function

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Abstract

Background: Evaluation of donor lung function relies on the arterial oxygen partial pressure to inspired oxygen fraction ratio ($\text{PaO}_2/\text{FiO}_2$) measurement. Hemodynamic, metabolic derangements, and therapeutic intervention occurring during brain dead observation may influence the evaluation of gas exchange.

Methods: We performed a mathematical analysis to explore the influence of the extrapulmonary determinants on the interpretation of $\text{PaO}_2/\text{FiO}_2$ in the brain-dead donor and during Ex-Vivo Lung Perfusion (EVLV).

Results: High FiO_2 and increased mixed venous oxygen saturation, caused by increased delivery and reduced consumption of oxygen, raise the $\text{PaO}_2/\text{FiO}_2$ despite substantial intrapulmonary shunt. Anemia does not modify the $\text{PaO}_2/\text{FiO}_2$ —intrapulmonary shunt relationship. During EVLV, the reduced artero-venous difference in oxygen content increases the $\text{PaO}_2/\text{FiO}_2$ without this corresponding to an optimal graft function, while the reduced perfusate oxygen-carrying capacity linearizes the $\text{PaO}_2/\text{FiO}_2$ —intrapulmonary shunt relationship.

Conclusions: Adopting $\text{PaO}_2/\text{FiO}_2$ to evaluate graft suitability for transplantation should account for extrapulmonary factors affecting its interpretation.

KEYWORDS

ex vivo lung perfusion, intrapulmonary shunt, lung transplantation, mixed venous oxygen saturation, multiorgan donor

1 | INTRODUCTION

The arterial oxygen partial pressure to inspired oxygen fraction ratio ($\text{PaO}_2/\text{FiO}_2$) is one of the primary criteria in evaluating lung donor suitability for transplantation. However, the hemodynamic and metabolic derangements, the ventilatory and resuscitation strategies adopted during

donor after brain-dead (DBD) management may impair the reliability of $\text{PaO}_2/\text{FiO}_2$ in reflecting the actual donor lung oxygenation capacity.

The DBD is usually characterized by a cardiocirculatory hyperdynamic state initiated by the catecholaminergic storm and sustained by exogenous vasopressor administration,¹ both increasing oxygen delivery. On

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the contrary, oxygen consumption decreases throughout DBD observation mainly due to loss of cerebral contribution to oxygen metabolism, hormone (thyroid hormone and cortisol) depletion, hypothermia (loss of thermoregulatory mechanisms), and reduced oxygen extraction because of the fall in tissue metabolic rate and absence of muscular activity.² The vascular dilatation and eventually diabetes *insipidus* lead to high-volume crystalloids resuscitation with possible subsequent further temperature decrease and hemodilution anemia. This imbalance between oxygen delivery and consumption increases mixed venous oxygen saturation (SvO₂).³ Increased SvO₂ might contribute to maintain arterial oxygenation in the normal range in spite of suboptimal lung function. During ex vivo lung perfusion (EVLP), the low hemoglobin concentration in the perfusate determines a linearization of the PaO₂/FIO₂ to intrapulmonary shunt relationship: A value of 300 mm Hg PaO₂/FIO₂ might mask an underlying considerable impairment of the graft gas exchange function. In this clinical scenario, the intrapulmonary shunt may better reflect the actual lung oxygenation function since it takes into account the actual mixed venous and arterial oxygen content. The aims of the present study are: (1) To elucidate how the derangements of oxygen delivery and consumption occurring in the multiorgan donor affect the PaO₂/FIO₂ interpretation. (2) To elucidate how different EVLP protocol-related settings affect the PaO₂/FIO₂ value.

2 | METHODS

In the present report, we exploited a validated mathematical model to critically evaluate the contribution of extrapulmonary determinants of gas exchange in the relationship between PaO₂/FIO₂ and intrapulmonary shunt.

2.1 | Mathematical model

The hemodynamic and metabolic parameters of the hypothetical brain-dead donor were derived from the available literature^{2,4} (Figure 1) and utilized as inputs of a mathematical model of body oxygenation (www.ecmomodel.unimi.it).⁵ This validated model can calculate both mixed venous and arterial oxygen content given the values of the primary independent determinants of patient oxygenation: cardiac output, total oxygen consumption, intrapulmonary shunt fraction, the fraction of inspired oxygen, serum hemoglobin, body temperature, arterial pH, and arterial partial pressure of carbon dioxide. The intrapulmonary shunt was considered an independent variable while PaO₂/FIO₂ was derived as a dependent variable by modulating separately: (1) FIO₂, (2) cardiac output, (3) total oxygen consumption, and (4) hemoglobin levels within clinically relevant ranges. The model explores the effect of a single variable while keeping the others constant.

Intrapulmonary shunt is thus calculated according to the standard formula:

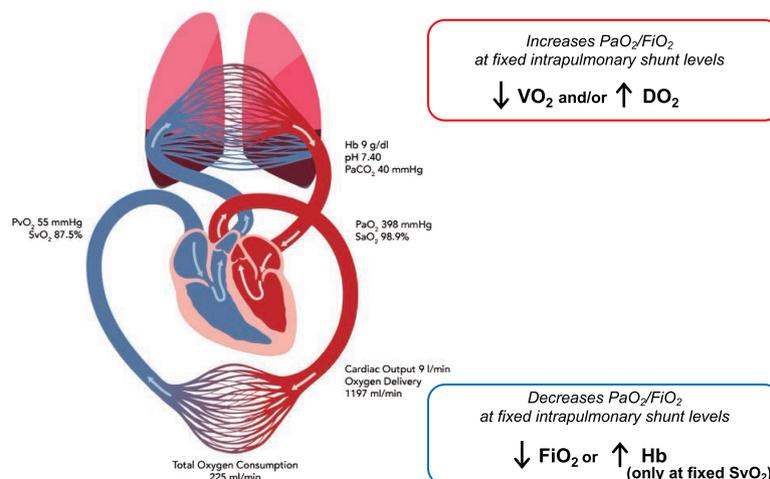


FIGURE 1 Gas exchange model in the brain-dead donor. The image illustrates the average values of the extrapulmonary determinants of PaO₂/FIO₂ used in the mathematical model to derive the venous and arterial oxygen content. The values adopted have been derived from the available literature: Cardiac output of 3.5–4.0 Lt/min/m² with a total oxygen delivery of 450–550 ml/min/m², and total oxygen consumption of 115–120 ml/min/m². In the present example, we calculated the estimated values in a 70 kg subject: The cardiac output is 9 L/min, the total oxygen consumption is 225 ml/min, the hemoglobin level is 9 g/dl, the arterial pH is 7.40, arterial partial pressure of carbon dioxide (PaCO₂) is 40 mm Hg. Assuming an intrapulmonary shunt level in the middle/high range (25%) this result in a PaO₂/FIO₂ value in the normal range (398 mm Hg), well above the cut-off for determination of donor lung suitability for transplantation. [Color figure can be viewed at wileyonlinelibrary.com]



$$\frac{Q_s}{Q_t} = \frac{(C_{cO_2} - C_{aO_2})}{(C_{cO_2} - C_{vO_2})}$$

where Q_s , shunting blood flow; Q_t , total blood flow; C_{cO_2} , pulmonary end-capillary O₂ content; C_{aO_2} , arterial O₂ content; C_{vO_2} , mixed venous O₂ content.

2.2 | Clinical data

IRB approval and patient-informed consent were not required due to the nature of the study reporting aggregated retrospectively collected data from isolated organs of previously deceased patients.

To assess the effect of reduced plasma oxygen-carrying capacity, we evaluated the gas exchange of all lung grafts treated with EVLP at our Institution between December 1, 2017 to June 30, 2021. The EVLP was run according to a protocol previously described⁶ with an open atrium technique, using a Steen™ Solution-based perfusate with a hematocrit between 10 and 15% and a target blood flow at 40% of the predicted donor cardiac output. We correlated the PaO₂/FiO₂ value to the intrapulmonary shunt levels measured hourly during EVLP. All gas exchange evaluations were performed at 100% FiO₂. Oxygen consumption, obtained by ventilating with the membrane lung with nitrogen, was kept constant (36 [33;41] mL/min) at each time point.

3 | RESULTS

Figure 2 illustrates the relationship between intrapulmonary shunt and PaO₂/FiO₂ at three predefined levels of respectively FiO₂ (Panel A), cardiac output (Panel B), total oxygen consumption (Panel C), and hemoglobin (Panel D).

1. By increasing FiO₂ up to 100%, venous admixture contribution to gas exchange is abolished thus increasing the PaO₂/FiO₂ value for any intrapulmonary shunt level. Above 30% intrapulmonary shunt the impact of FiO₂ level on PaO₂/FiO₂ is minimal.
2. Both increasing cardiac output and/or reducing oxygen consumption moves to the right of the intrapulmonary shunt to PaO₂/FiO₂ relationship. This implies that for a similar PaO₂/FiO₂ level the patients with the higher cardiac output and/or the lower oxygen consumption have the worse intrapulmonary shunt.
3. In the setting of increased SvO₂, reducing serum hemoglobin level marginally affects the PaO₂/FiO₂ for each intrapulmonary shunt value: Both the SvO₂ and the

blood oxygen-carrying capacity are reduced thus neutralizing their reciprocal effect.

Twenty EVLP procedures have been included in the study, 12 from donors after cardiocirculatory death and 8 from extended-criteria brain-dead donors. Measuring intrapulmonary shunt during EVLP from real clinical data, we observed a significant and linear correlation between intrapulmonary shunt and PaO₂/FiO₂ (p -value <0.0001; R^2 0.892; Equation: PaO₂/FiO₂ = 739–795*intrapulmonary shunt), Figure 3 Panel A. Due to the curve slope, PaO₂/FiO₂ values between 400 and 500 mmHg correspond to intrapulmonary shunt about 30 to 40%. When simulating by mathematical modeling to run the EVLP at lowering hemoglobin level while keeping fixed the SvO₂ (Figure 3 Panel B), we observed an upright shift of the intrapulmonary shunt to PaO₂/FiO₂ relationship: during acellular EVLP PaO₂/FiO₂ of 350 corresponds to about 55% intrapulmonary shunt.

4 | DISCUSSION

The main findings of the present study are:

1. Lung oxygenation capacity both in the multiorgan donor and during EVLP should be evaluated at high FiO₂ in order to avoid the confounding effect of venous admixture.
2. The multiorgan donors are predisposed to develop a high SvO₂ state due to reduced oxygen consumption and increased oxygen delivery. A high SvO₂ state increases the PaO₂/FIO₂ without this corresponding to an optimal graft oxygenation capacity.
3. During EVLP, the low oxygen consumption and hemoglobin levels determine that high PaO₂/FiO₂ (>300mmHg) corresponds to high intrapulmonary shunt levels.

The PaO₂/FiO₂ is used worldwide as the ultimate criterion for judgment of graft suitability for transplantation due to the—apparently—simplicity of its interpretation. However, multiple reports did not find an association between early lung allograft function and donor oxygenation.^{7,8} In critically ill patients, intrapulmonary shunt represents the gold standard for the evaluation of lung oxygenation capacity. In fact, intrapulmonary shunt, differently from the most widely adopted PaO₂/FiO₂, reflects only the lung oxygenation capacity without being affected by oxygen delivery and consumption. Conversely, the main disadvantage of measuring intrapulmonary shunt, at least in the brain-dead donor, is the need of pulmonary artery catheter placement, which is not commonly used for the

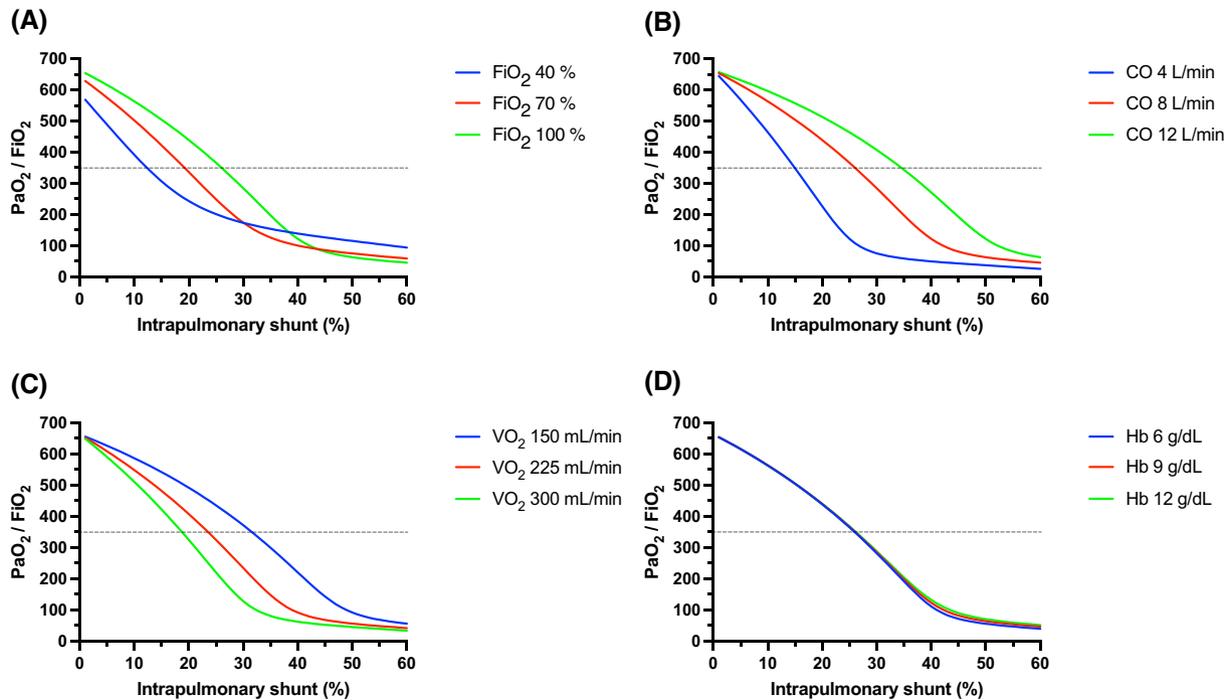


FIGURE 2 Extrapulmonary determinants of PaO₂/FiO₂ in the brain-dead donor. *Panel A:* By progressively increasing the FiO₂, and abolishing the venous admixture contribution to gas exchange, the PaO₂/FiO₂ value is increased for any intrapulmonary shunt level assessed. However, above a level of the intrapulmonary shunt of 30% the FiO₂ level minimally affects PaO₂/FiO₂. In the setting of the brain-dead donor, all factors determining an increase in mixed venous oxygen saturation cause an increase in the PaO₂/FiO₂ value without this corresponding to a decrease in intrapulmonary shunt fraction. *Panel B:* Increasing oxygen delivery by rising cardiac output at a constant total oxygen consumption rate increases the PaO₂/FiO₂ for any value of intrapulmonary shunt. *Panel C:* Decreasing total oxygen consumption at a constant oxygen delivery rate increases the PaO₂/FiO₂ for any value of intrapulmonary shunt. *Panel D:* Varying hemoglobin concentration does not affect the PaO₂/FiO₂ value for any value of intrapulmonary shunt. The dashed line marks the values of intrapulmonary shunt obtained at a PaO₂/FiO₂ of 350 mm Hg, cut-off for determination of donor lung suitability for transplantation. CO, cardiac output; FiO₂, fraction of inspired oxygen; Hb, hemoglobin level; PaO₂/FiO₂, Arterial partial pressure of oxygen to fraction of inspired oxygen ratio; VO₂, Total oxygen consumption. [Color figure can be viewed at wileyonlinelibrary.com]

hemodynamic management of brain-injured patients. In the present brief report, we elucidated the magnitude of PaO₂/FiO₂ changes when varying the main extrapulmonary determinants of arterial oxygenation.

The complex relationship between FiO₂ and PaO₂/FiO₂ has been widely investigated⁹: the oxyhemoglobin dissociation curve and the presence of lung regions with low ventilation-perfusion ratio determine a down-leftward shift of the intrapulmonary shunt to PaO₂/FiO₂ relationship at low (<50%) FiO₂. Evaluating PaO₂/FiO₂ at a standardized FiO₂ in the high range (>70%) minimizes the confounding effect of venous admixture.

Both seminal clinical paper and experimental data showed multiorgan donors to have an increased oxygen delivery and reduced oxygen consumption.¹⁰ Using a physiology-based mathematical model, we demonstrated that the elevated oxygen delivery rate and the reduced oxygen consumption that occurs during brain dead result in high SvO₂ and low artero-venous O₂ difference. In this scenario, intermediate-high PaO₂/FiO₂ levels correspond to a significant amount of intrapulmonary shunt.¹¹

The clinical implication of the present findings is that whenever a high cardiac output is documented (for example by echocardiography) a donor lung with borderline PaO₂/FiO₂ (i.e. 300–350 mm Hg) should be more carefully evaluated considering parameters other than arterial oxygenation. The most recent literature validated the use of donor respiratory system compliance instead of the donor PaO₂/FiO₂ levels for predicting graft post-operative function.¹²

The Toronto group demonstrated that PaO₂/FiO₂ represents only a late sign of organ dysfunction during EVLP.¹³ This observation should be obvious if we consider perfusate oxygen content instead of oxygen partial pressure. The absence or low level of hemoglobin determines a low perfusate oxygen-carrying capacity, while the low oxygen consumption level determines a reduced venous to arterial oxygen content difference. In this scenario even in the case of a limited number of functional alveolar units, the diffusion of a little amount of oxygen is able to produce a significant rise in perfusate PO₂. In our EVLP case series, a value of PaO₂/FiO₂ of 350 mm Hg corresponds

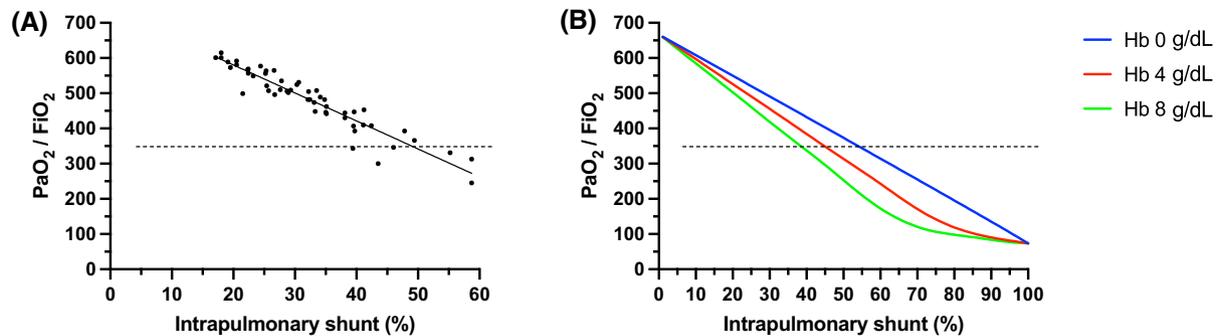


FIGURE 3 Intrapulmonary shunt and PaO₂/FiO₂ relationship during EVLP. Data from clinical EVLP show an almost linear upright the shifted relationship between intrapulmonary shunt and PaO₂/FiO₂ (*Panel A*). Each point represents one of the measurements of gas exchange performed hourly during each EVLP procedure. The reduced a-v O₂ content due to the high venous oxygen saturation (>87%) and the reduced perfusate oxygen-carrying capacity determines that PaO₂/FiO₂ between 400 to 500 mm Hg corresponds to intrapulmonary shunt between 30 to 40%. *Panel B*: Decreasing hemoglobin level while “artificially” keeping constant the SvO₂ unmasks the effect of the reduced oxygen-carrying capacity: When decreasing the perfusate hemoglobin concentration the PaO₂/FiO₂ is increased for any value of intrapulmonary shunt. The dashed line marks the values of intrapulmonary shunt obtained at a PaO₂/FiO₂ of 350 mm Hg, cut-off for determination of donor lung suitability for transplantation. Hb, hemoglobin level; PaO₂/FiO₂, Arterial partial pressure of oxygen to fraction of inspired oxygen ratio. [Color figure can be viewed at wileyonlinelibrary.com]

to a shunt fraction of 45%. The clinical implication of the present observation is that contrarily to what has been reported in previous studies, the PaO₂/FiO₂ should not be used to compare donor lung function in-vivo vs. during EVLP¹⁴ and between different EVLP protocols (i.e., cellular vs acellular and/or low vs high blood flow).¹⁵ Due to the easiness of measuring intrapulmonary shunt during EVLP, it might provide useful information to evaluate graft function. Unfortunately, we are currently unable to provide a definitive intrapulmonary shunt threshold to define lung acceptability for transplantation, this should be the object of further investigations. The course of lung compliance and pulmonary vascular resistance over 4 h of EVLP might help to define lung suitability for transplantation,^{16,17} particularly when non-ideal gas exchanges are measured.

5 | CONCLUSIONS

Both in brain-dead donors and during EVLP, evaluating donor lung function by means of the PaO₂/FiO₂, despite being practical, might be misleading. Increased SvO₂ values and/or reduced oxygen-carrying capacity result in PaO₂/FiO₂ in the normal-high range without this corresponding to a low intrapulmonary shunt level. Clinicians should be aware of the extrapulmonary determinants of PaO₂/FiO₂ in order to personalize the oxygenation criteria threshold for graft suitability for transplantation.

AUTHOR CONTRIBUTIONS

Jacopo Fumagalli, Sebastiano Maria Colombo, Vittorio Scaravilli, and Alberto Zanella conceived the study.

Francesca Gori and Jacopo Fumagalli collected EVLP data; Jacopo Fumagalli and Sebastiano Maria Colombo analyzed the data; Jacopo Fumagalli, Sebastiano Maria Colombo, and Vittorio Scaravilli drafted the original version of the manuscript; Alberto Zanella, Antonio Pesenti, and Giacomo Grasselli revised the manuscript critically; all authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter discussed in this manuscript.

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