Received: 1 April 2022 | Revised: 4 June 2022 | Accepted: 17 June 2022

DOI: 10.1111/aor.14350

Artificial Organs WILEY

THOUGHTS & PROGRESS

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

Jacopo Fumagalli[1] | **Sebastiano Maria Colombo**[1] | **Vittorio Scaravilli**[1,2] | **Francesca Gori**[1] | **Antonio Pesenti**[1,3] | **Alberto Zanella**[1,3] | **Giacomo Grasselli**[1,3]

[1]Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Milan, Italy

[3]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Correspondence
Alberto Zanella, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Padiglione Litta, Via della Commenda 16, Milan 20122, Italy.
Email: alberto.zanella1@unimi.it

Funding information
Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico; Università degli Studi di Milano

Abstract

Background: Evaluation of donor lung function relies on the arterial oxygen partial pressure to inspired oxygen fraction ratio (PaO_2/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 PaO_2/FiO_2 in the brain-dead donor and during Ex-Vivo Lung Perfusion (EVLP).

Results: High FiO_2 and increased mixed venous oxygen saturation, caused by increased delivery and reduced consumption of oxygen, raise the PaO_2/FiO_2 despite substantial intrapulmonary shunt. Anemia does not modify the PaO_2/FiO_2—intrapulmonary shunt relationship. During EVLP, the reduced artero-venous difference in oxygen content increases the PaO_2/FiO_2 without this corresponding to an optimal graft function, while the reduced perfusate oxygen-carrying capacity linearizes the PaO_2/FiO_2—intrapulmonary shunt relationship.

Conclusions: Adopting PaO_2/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 (PaO_2/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 PaO_2/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

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 (SvO$_2$).[3] Increased SvO$_2$ 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 PaO$_2$/FiO$_2$ to intrapulmonary shunt relationship: A value of 300 mm Hg PaO$_2$/FiO$_2$ might mask an underling 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 PaO$_2$/FiO$_2$ interpretation. (2) To elucidate how different EVLP protocol-related settings affect the PaO$_2$/FiO$_2$ 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 PaO$_2$/FiO$_2$ 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 PaO$_2$/FiO$_2$ was derived as a dependent variable by modulating separately: (1) FiO$_2$, (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:

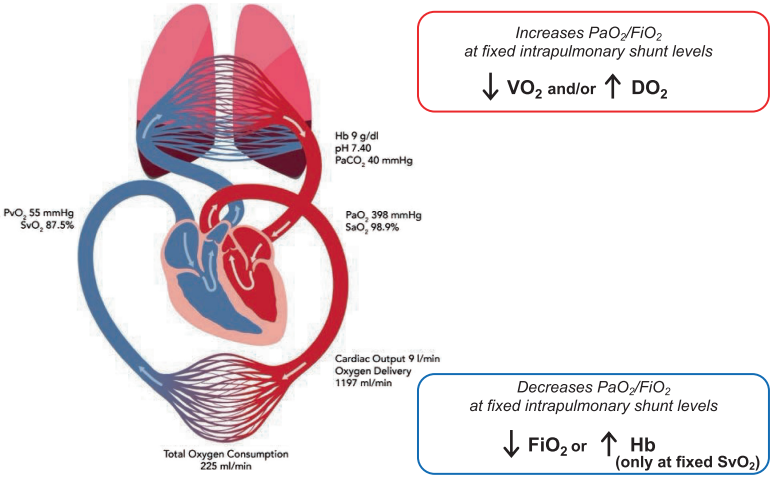

FIGURE 1 Gas exchange model in the brain-dead donor. The image illustrates the average values of the extrapulmonary determinants of PaO$_2$/FiO$_2$ used in the mathematical model to derive the venous and arterial oxygen content. The values adopted have been derived from the available literature: Cardiac output of 3.5–4.0 Lt/min/m^2 with a total oxygen delivery of 450–550 ml/min/m^2, and total oxygen consumption of 115–120 ml/min/m^2. 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 (PaCO$_2$) is 40 mm Hg. Assuming an intrapulmonary shunt level in the middle/high range (25%) this result in a PaO$_2$/FiO$_2$ 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]

$$\frac{Qs}{Qt} = \frac{(CcO_2 - CaO_2)}{(CcO_2 - CvO_2)}$$

where Qs, shunting blood flow; Qt, total blood flow; CcO_2, pulmonary end-capillary O_2 content; CaO_2, arterial O_2 content; CvO_2, mixed venous O_2 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 described[6] 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 PaO_2/FiO_2 value to the intrapulmonary shunt levels measured hourly during EVLP. All gas exchange evaluations were performed at 100% FiO_2. 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 PaO_2/FiO_2 at three predefined levels of respectively FiO_2 (Panel A), cardiac output (Panel B), total oxygen consumption (Panel C), and hemoglobin (Panel D).

1. By increasing FiO_2 up to 100%, venous admixture contribution to gas exchange is abolished thus increasing the PaO_2/FiO_2 value for any intrapulmonary shunt level. Above 30% intrapulmonary shunt the impact of FiO_2 level on PaO_2/FiO_2 is minimal.
2. Both increasing cardiac output and/or reducing oxygen consumption moves to the right of the intrapulmonary shunt to PaO_2/FiO_2 relationship. This implies that for a similar PaO_2/FiO_2 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 SvO_2, reducing serum hemoglobin level marginally affects the PaO_2/FiO_2 for each intrapulmonary shunt value: Both the SvO_2 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 PaO_2/FiO_2 (p-value <0.0001; R^2 0.892; Equation: PaO_2/FiO_2 = 739−795*intrapulmonary shunt), Figure 3 Panel A. Due to the curve slope, PaO_2/FiO_2 values between 400 and 500 mm Hg 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 SvO_2 (Figure 3 Panel B), we observed an upright shift of the intrapulmonary shunt to PaO_2/FiO_2 relationship: during acellular EVLP PaO_2/FiO_2 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 FiO_2 in order to avoid the confounding effect of venous admixture.
2. The multiorgan donors are predisposed to develop a high SvO_2 state due to reduced oxygen consumption and increased oxygen delivery. A high SvO_2 state increases the PaO_2/FIO_2 without this corresponding to an optimal graft oxygenation capacity.
3. During EVLP, the low oxygen consumption and hemoglobin levels determine that high PaO_2/FiO_2 (>300 mm Hg) corresponds to high intrapulmonary shunt levels.

The PaO_2/FiO_2 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 PaO_2/FiO_2, 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

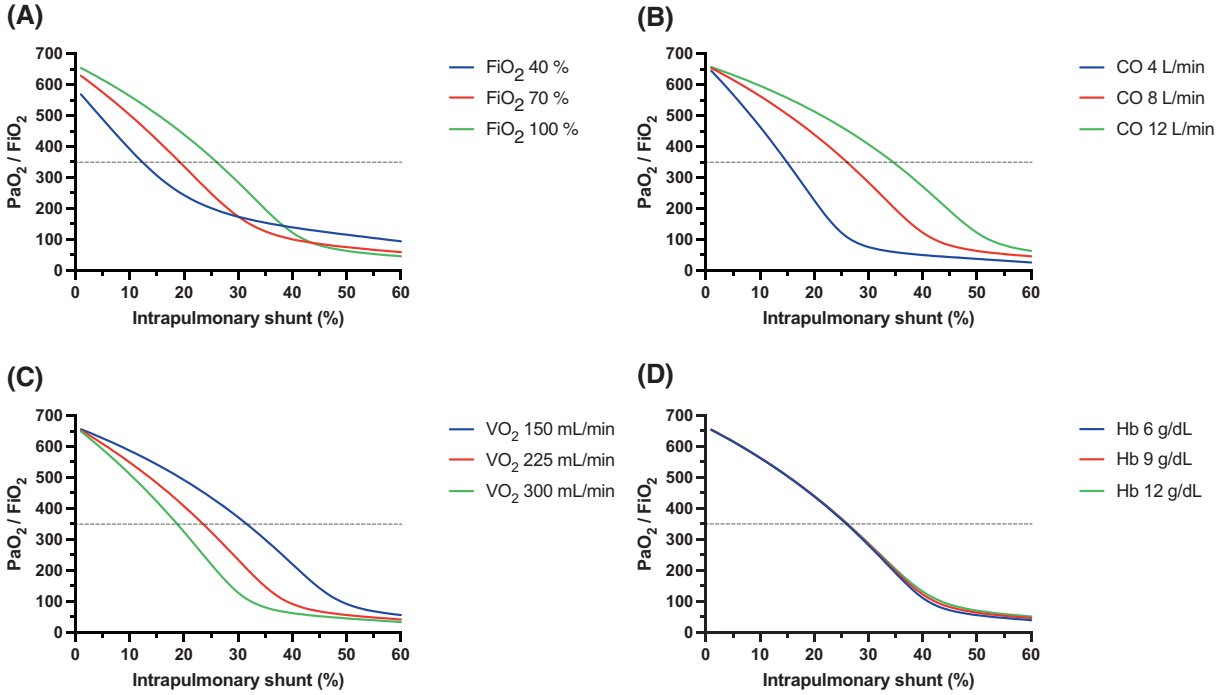

FIGURE 2 Extrapulmonary determinants of PaO_2/FiO_2 in the brain-dead donor. *Panel A*: By progressively increasing the FiO_2, and abolishing the venous admixture contribution to gas exchange, the PaO_2/FiO_2 value is increased for any intrapulmonary shunt level assessed. However, above a level of the intrapulmonary shunt of 30% the FiO_2 level minimally affects PaO_2/FiO_2. In the setting of the brain-dead donor, all factors determining an increase in mixed venous oxygen saturation cause an increase in the PaO_2/FiO_2 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 PaO_2/FiO_2 for any value of intrapulmonary shunt. *Panel C*: Decreasing total oxygen consumption at a constant oxygen delivery rate increases the PaO_2/FiO_2 for any value of intrapulmonary shunt. *Panel D*: Varying hemoglobin concentration does not affect the PaO_2/FiO_2 value for any value of intrapulmonary shunt. The dashed line marks the values of intrapulmonary shunt obtained at a PaO_2/FiO_2 of 350 mm Hg, cut-off for determination of donor lung suitability for transplantation. CO, cardiac output; FiO_2, fraction of inspired oxygen; Hb, hemoglobin level; PaO_2/FiO_2, Arteral partial pressure of oxygen to fraction of inspired oxygen ratio; VO_2, 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 PaO_2/FiO_2 changes when varying the main extrapulmonary determinants of arterial oxygenation.

The complex relationship between FiO_2 and PaO_2/FiO_2 has been widely investigated[9]: 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 PaO_2/FiO_2 relationship at low (<50%) FiO_2. Evaluating PaO_2/FiO_2 at a standardized FiO_2 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 SvO_2 and low artero-venous O_2 difference. In this scenario, intermediate-high PaO_2/FiO_2 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 PaO_2/FiO_2 (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 PaO_2/FiO_2 levels for predicting graft post-operative function.[12]

The Toronto group demonstrated that PaO_2/FiO_2 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 PO_2. In our EVLP case series, a value of PaO_2/FiO_2 of 350 mm Hg corresponds

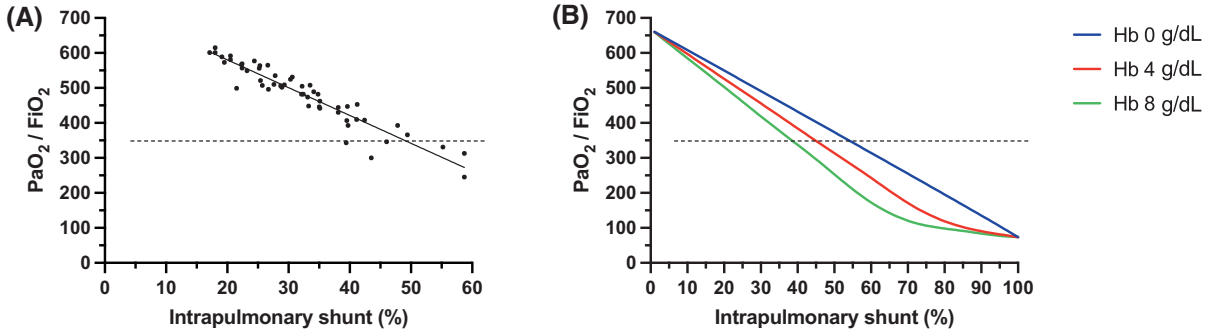

FIGURE 3 Intrapulmonary shunt and PaO_2/FiO_2 relationship during EVLP. Data from clinical EVLP show an almost linear upright the shifted relationship between intrapulmonary shunt and PaO_2/FiO_2 (*Panel A*). Each point represents one of the measurements of gas exchange performed hourly during each EVLP procedure. The reduced a-v O_2 content due to the high venous oxygen saturation (>87%) and the reduced perfusate oxygen-carrying capacity determines that PaO_2/FiO_2 between 400 to 500 mm Hg corresponds to intrapulmonary shunt between 30 to 40%. *Panel B*: Decreasing hemoglobin level while "artificially" keeping constant the SvO_2 unmasks the effect of the reduced oxygen-carrying capacity: When decreasing the perfusate hemoglobin concentration the PaO_2/FiO_2 is increased for any value of intrapulmonary shunt. The dashed line marks the values of intrapulmonary shunt obtained at a PaO_2/FiO_2 of 350 mm Hg, cut-off for determination of donor lung suitability for transplantation. Hb, hemoglobin level; PaO_2/FiO_2, 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 PaO_2/FiO_2 should not be used to compare donor lung function in-vivo vs. during EVLP[14] 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 PaO_2/FiO_2, despite being practical, might be misleading. Increased SvO_2 values and/or reduced oxygen-carrying capacity result in PaO_2/FiO_2 in the normal-high range without this corresponding to a low intrapulmonary shunt level. Clinicians should be aware of the extrapulmonary determinants of PaO_2/FiO_2 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.

ACKNOWLEDGMENTS

We thank Lucia Maria Colombo for providing graphical technical support. Open access funding provided by BIBLIOSAN. [Correction added on 2 December 2022, after first online publication: funding statement has been added.]

FUNDING INFORMATION

The study was funded by the Department of Anesthesia and Critical Care Medicine, IRCCS Ca′ Granda Ospedale Maggiore Policlinico di Milano and Department of Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano. The study was partially funded by the Italian Ministry of Health - Current Research IRCCS. The study was supported by a fund dedicated to research derived from the 5x1000 fund donated to the Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico.

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.

ORCID

Jacopo Fumagalli https://orcid.org/0000-0002-8303-4796
Sebastiano Maria Colombo https://orcid.org/0000-0002-9612-5187
Vittorio Scaravilli https://orcid.org/0000-0003-0877-7626
Francesca Gori https://orcid.org/0000-0001-8330-5077
Antonio Pesenti https://orcid.org/0000-0003-2593-729X
Alberto Zanella https://orcid.org/0000-0002-2967-2527
Giacomo Grasselli https://orcid.org/0000-0002-1735-1400

REFERENCES

1. Cooper DK, Novitzky D, Wicomb WN. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. Ann R Coll Surg Engl. 1989;71(4):261–6.
2. Langeron O, Couture P, Mateo J, Riou B, Pansard JL, Coriat P. Oxygen consumption and delivery relationship in brain-dead organ donors. Br J Anaesth. 1996;76(6):783–9. https://doi.org/10.1093/bja/76.6.783
3. Dauri M, Turani F, Andreozzi G, Celeste GF, Colella DF, Zupancich E, et al. Monitoring of mixed venous oxygen saturation in multiorgan donors. Preliminary data. Minerva Anestesiol. 1991;57(12 Suppl):139–46.
4. Depret J, Teboul JL, Benoit G, Mercat A, Richard C. Global energetic failure in brain-dead patients. Transplantation. 1995;60(9):966–71.
5. Zanella A, Salerno D, Scaravilli V, Giani M, Castagna L, Magni F, et al. A mathematical model of oxygenation during venovenous extracorporeal membrane oxygenation support. J Crit Care. 2016;36:178–86. https://doi.org/10.1016/j.jcrc.2016.07.008
6. Fumagalli J, Rosso L, Gori F, Morlacchi LC, Rossetti V, Tarsia P, et al. Early pulmonary function and mid-term outcome in lung transplantation after ex-vivo lung perfusion - a single-center, retrospective, observational, cohort study. Transpl Int. 2020;33(7):773–85. https://doi.org/10.1111/tri.13606
7. Sommers KE, Griffith BP, Hardesty RL, Keenan RJ. Early lung allograft function in twin recipients from the same donor: risk factor analysis. Ann Thorac Surg. 1996;62(3):784–90. https://doi.org/10.1016/s0003-4975(96)00371-2
8. Thabut G, Mal H, Cerrina J, Dartevelle P, Dromer C, Velly JF, et al. Influence of donor characteristics on outcome after lung transplantation: a multicenter study. J Heart Lung Transplant. 2005;24(9):1347–53. https://doi.org/10.1016/j.healun.2004.10.016
9. Whiteley JP, Gavaghan DJ, Hahn CEW. Variation of venous admixture, SF6 shunt, PaO2, and the PaO2/FIO2 ratio with FIO2. Br J Anaesth. 2002;88(6):771–8. https://doi.org/10.1093/bja/88.6.771
10. Zaky A, Pretto EA, Earle SA, et al. Hemodynamic and metabolic efficacy of dopamine versus norepinephrine in a brain-dead swine model. Liver Transpl. 2008;14(9):1266–72. https://doi.org/10.1002/lt.21535
11. Martyn JA, Aikawa N, Wilson RS, Szyfelbein SK, Burke JF. Extrapulmonary factors influencing the ratio of arterial oxygen tension to inspired oxygen concentration in burn patients. Crit Care Med. 1979;7(11):492–6. https://doi.org/10.1097/00003246-197911000-00003
12. Benazzo A, Schwarz S, Frommlet F, Sinn K, Schweiger T, Klikovits T, et al. Donor ventilation parameters as predictors for length of mechanical ventilation after lung transplantation: Results of a prospective multicenter study. J Heart Lung Transplant. 2021;40(1):33–41. https://doi.org/10.1016/j.healun.2020.10.008
13. Yeung JC, Cypel M, Machuca TN, Koike T, Cook DJ, Bonato R, et al. Physiologic assessment of the ex vivo donor lung for transplantation. J Heart Lung Transplant. 2012;31(10):1120–6. https://doi.org/10.1016/j.healun.2012.08.016
14. Cypel M, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med. 2011;364(15):1431–40. https://doi.org/10.1056/NEJMoa1014597
15. Okamoto T, Wheeler D, Farver CF, McCurry KR. Transplant suitability of rejected human donor lungs with prolonged cold ischemia time in low-flow acellular and high-flow cellular ex vivo lung perfusion systems. Transplantation. 2019;103(9):1799–808. https://doi.org/10.1097/TP.0000000000002667
16. Di Nardo M, Del Sorbo L, Sage A, et al. Predicting donor lung acceptance for transplant during ex vivo lung perfusion: the EX vivo lung PerfusIon pREdiction (EXPIRE). Am J Transplant. 2021;21(11):3704–13. https://doi.org/10.1111/ajt.16616
17. Spratt JR, Mattison LM, Iaizzo PA, Meyer C, Brown RZ, Iles T, et al. Lung transplant after prolonged ex vivo lung perfusion: predictors of allograft function in swine. Transpl Int. 2018;31(12):1405–17. https://doi.org/10.1111/tri.13315

How to cite this article: Fumagalli J, Colombo SM, Scaravilli V, Gori F, Pesenti A, Zanella A, Limitations of arterial partial pressure of oxygen to fraction of inspired oxygen ratio for the evaluation of donor lung function. Artif. Organs. 2022;46:2313–2318. https://doi.org/10.1111/aor.14350