Peer Review File

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Reviewer A

Comment 1: However, the framing at the start of the report (33-36) is not consistently reinforced throughout, and sometimes skips between these steps. A clearer structure and addressing the points below would improve the quality of this article significantly.

Reply 1: We agree, that a clearer structure with emphasis on this concept would improve the quality of our article. We added a new paragraph to first explain the model by Wagner and then explain how we adapted it to the special situation of ECMO with total lung replacement later.

Changes in Text 1: page 3, lines 65-81:

The global convective oxygen delivery (DO_2) can be described as

$DO_2 = Q \times CaO_2$

The main determinants of CaO_2 are hemoglobin concentration (Hb) and arterial oxygen saturation (SaO_2).

The oxygen consumption according to the Fick principle can be described as

$VO_2 = Q \times (CaO_2 - CvO_2)$

The oxygen delivery from the capillary to the mitochondrium with a certain diffusion capacity D can be described as

$VO_2 = D \times (PcapO_2 - PmitO_2)$

If the partial pressure of oxygen at the mitochondrium can be neglected and the partial pressure of oxygen in the terminal capillaries is proportional to venous partial pressure of oxygen with a constant factor k, this can be described as

$VO_2 = D \times k \times PvO_2$

If the dissolved oxygen is in equilibrium with the oxygen bound to hemoglobin following the sigmoid oxygen dissociation curve, the connective and diffusive oxygen delivery can be plotted on the same graph where VO_2 is the ordinate and PvO_2 is the abscissa. This model is consistent with the current understanding of the physiology of oxygen delivery.(4)

Comment 2: suggest “in sequence” or “in series” rather than “in a row”

Reply 2: We made the recommended change

Changes in Text 2: page 3, line 62: “Occur in sequence”

Comment 3: 46-52 – The description of this relationship could be clearer. I suggest first explicitly addressing how ECMO fully oxygenates all blood passing through the circuit, and then relating this back to the previously illustrated known oxygen saturation and delivery formula, in order to have consistent framing.

Reply 3: We made the recommended changes by first describing the model by Wagner (as described in Reply 1) and then specified how all blood passing through the circuit is oxygenated and how this applies to our model.

Changes in Text 3: page 4, line 84, lines 94-99:

Because we consider the ECMO oxygenator to be capable of fully oxygenating all blood passing through the oxygenator. This is only true, if the lung function can be neglected and the lung does not take part in gas exchange.

Further changes in Text:

1. Situation A : High CO (QA) , low CaO_2 (CaO_2A), $DO_2A = QA \times CaO_2A$; Situation B: Low CO (QB), higher CaO_2 (CaO_2B), $DO_2B = QB \times CaO_2B$
2. Under the conditions of a CO that is significantly higher than the ECMO flow, a properly functioning oxygenator and minimal recirculation we consider $DO_2A = DO_2B$
3. Oxygen consumption remains constant and equal in both situations $VO_2A = VO_2B = QA \times (CaO_2A\text{-}CvO_2A) = QB \times (CaO_2B - CvO_2B)$

Comment 4: space between 'these' and 'situations'
Reply 4: we inserted the space as recommended
Changes in Text 4: page 4, line 91: space inserted

Comment 5: A brief description of Wagner's model would be helpful here; it is inconsistent to fully describe the formula for delivery of oxygen and then give no context for Wagner's model before jumping into variables not previously introduced
Reply 5: we inserted a description of the model as described in Response 1
Changes in Text 5: as "Changes in Text 1"

Comment 6: remove comma after 'we see'
Reply 6: The comma was removed
Changes in Text 6: page 5, line 121: comma removed

Comment 7: citation missing for the research mentioned
Reply 7: The appropriate citations were included
Changes in Text 7: page 5, line 123: Citations were inserted and bibliography was updated

Comment 8: either a typo or grossly mischaracterized; one study mentioned use a value of PaO2 of 60mmHg, another used SpO2 not PaO2, and the last a PaO2 of 55-70mmHg.
Reply 8: This is truly a typo. We made the appropriate change and apologize for this confusing mistake.
Changes in Text 8: page 6, line 125-127: While values for PaO_2 around 60mmHg have been considered safe in past clinical trials (HOT- ICU, ICU-ROX), the $LOCO_2$ trial with a target of 55-70mmHg in the conservative oxygen group was stopped early because of an increased number in mesenterial ischemia (8–10).

Comment 9: "risc" is assumed to be a typo for "risk"
Reply 9: This is a typo, we made the appropriate correction
Changes in Text 9: page 6, line 132: risc is changed to risk

Reviewer B
Comment 1: - both Q en Ca are only written as an abbreviation. Please adjust. (Line 40 en 41)
Reply 1: We made the appropriate adjustments
Changes in Text 1: page 3, line 66: Ca: arterial oxygen content, Q: Cardiac output

Comment 2: line 57 thesesituations needs a space in between
Reply 2: We inserted the space
Changes in Text 2: page 4 line 91: space inserted

Comment 3: line 101 shouldn't "risc" be adjusted to "risk"?
Reply 3: We corrected this mistake
Changes in Text 3: page 6, line 132: risc changed to risk

Comment 4: However, the controverse also takes into account the contribution of some lung function which will be decreased by lowering the cardiac output as well as recirculation which might be increased by lowering the cardiac output (https://doi.org/10.1016/j.jcrc.2019.07.016). In fact these are all arguments which affect the convective DO2 (line 103) and therefore do not change your message. However, the understanding of the complexity of the debate as well as the complexity of finding the right cut-off for CO, would benefit by adding these arguments.
Reply 4: We fully agree, that in the context of real-life application of such a concept, these issues have to be taken into account. We therefore included these points in our discussion and cited the appropriate references. We thank you for this suggestion. In our introductory sentences, we also emphasized, that this concept is for cases with a total loss of lung function.
Changes in Text 4: page 6, line 134-139:
If there is some lung function left, this concept may not apply, since the potential influence of changes in cadiac output on the ventilation/perfusion mismatch have to be taken into account.(13) Furthermore especially in the context of a femoro- jugular cannulation, recirculation might increase. Our concept therefore only applies to a situation, where minimal recirculation can be achieved as with a bi-caval dual lumen cannula. In this case recirculation may be negligible(14).

Reviewer C
Comment 1: I must admit that I did not completely understand the Wagner Model, even when referring to the referenced manuscript.
Reply 1: We expanded our explanation of the original model and separated these explanations from our additional assumptions to improve the clarity. We further added two further references with detailed explanations to improve clarity.
Changes in Text 1: page 3 line 58- p4 line 81:
An integrated physiological model of tissue oxygenation describes oxygen delivery as process of multiple steps: Diffusion of the oxygen from the alveolus to the pulmonary capillary, convective transport via perfusion with oxygen mostly bound to hemoglobin (Hb), diffusion from capillary through tissue to the mitochondrium. As all steps occur in sequence, a limitation can occur on each of these steps.(1–6)
We will first describe the integration of oxygen transport during convection and diffusion according to this model.
The global convective oxygen delivery (DO_2) can be described as
$DO_2 = Q \times CaO_2$ (Q: Cardiac Output; CaO2: Arterial oxygen content)The main determinants of CaO_2 are hemoglobin concentration (Hb) and arterial oxygen saturation (SaO_2).

The oxygen consumption (VO2) according to the Fick principle can be described as
$VO_2 = Q \times (CaO_2 - CvO_2)$; (CvO2: Venous oxygen content)
The oxygen delivery from the capillary to the mitochondrium with a certain diffusion capacity D can be described as
$VO_2 = D \times (PcapO_2 - PmitO_2)$ (PcapO2: Oxygen partial pressure in the capillaries, PmitO2: Oxygen partial pressure at the mitochondrium)
If the partial pressure of oxygen at the mitochondrium can be neglected and the partial pressure of oxygen in the terminal capillaries is proportional to venous partial pressure of oxygen with a constant factor k, this can be described as
$VO_2 = D \times k \times PvO_2$ (PvO_2: Venous oxygen partial pressure)
If the dissolved oxygen is in equilibrium with the oxygen bound to hemoglobin following the sigmoid oxygen dissociation curve, the connective and diffusive oxygen delivery can be plotted on the same graph where VO_2 is the ordinate and PvO_2 is the abscissa. This model is consistent with the current understanding of the physiology of oxygen delivery.(6)

Comment 2: The effect of PaO2 on the ease with which hemoglobin releases oxygen, however, does suggest that there may be a window within the oxygen: hemoglobin dissociation curve in which the deleterious effect of decreasing cardiac output is outweighed by the increase in hemoglobin-bound oxygen. Within this window, likely located in the mid to low range of the steep art of the oxygen: hemoglobin dissociation curve, increasing hemoglobin-bound oxygen by dropping cardiac output to more closely approximate maximal ECMO flow may improve overall oxygen delivery.
Reply 2: The point is raised, that the effect of decreasing cardiac output is deleterious. We think that the current evidence regarding the use of short acting beta blockers in states of high cardiac output does not support a deleterious effect. Since the study by Morelli et al published in JAMA (DOI: 10.1001/jama.2013.278477) multiple trials have been performed regarding the use of beta blockers. A current review and meta analysis (doi: 10.1097/MD.0000000000029820) also supports the safety. Since the application of beta blockers in this condition is not a standard practice, we agree that safety concerns should be taken into consideration. We therefore added the statement, that short acting beta blockers like esmolol should be used in case adverse events are observed.
Changes in Text 2: page 6, line 132- 133: The use of a short acting medication like esmolol is preferable in this situation in cases where adverse events are observed.

Comment 3: Unfortunately, the theoretical nature of the argument makes it difficult to know whether the relative locations and slopes on the presented convective transport lines in Figure 1 are realistic or not. Similarly, the slow of the diffusion line is likely subject of arbitrary positioning.
I would like to understand how the particular slopes for the red and blue line, as well as the slope for the diffusion line, were chosen. Are they representations clinically relevant VO2 and PVO2 values?
Reply 3: We fully agree that we have no data to justify a precise position of our graphs. Because of this, there is no scale on the graph.

But to support our argument, it is the relationship between the red and the blue line, that is of significance. We explained that for any given VO_2 (broken line in Figure 1) the PvO_2 in situation A will be lower than the PvO_2 in situation B, because the oxygen content in any given volume of blood will be higher in situation B. The common origin of both lines on the ordinate is explained by the fact, that the maximal VO_2 is identical because the maximal DO_2 is identical. The shape of the red and blue lines is sigmoidal because of the hemoglobin dissociation curve.
The direction of the diffusion line must be a straight line with a positive slope. We therefore do not consider the positioning to be arbitrary.
We agree, that only if the appropriate data is generated in future research, we can conclude, if the changes predicted by our model have a clinically meaningful effect. We included this statement in our discussion.
Changes in Text 3: page 6, line 150: Further data is needed to evaluate whether the effects predicted by this model have a clinically meaningful effect.

Reviewer D

Comment 1: The authors considered that Delivery O2-A = Delivery O2-B, which is the starting point of their demonstration. However, changes of Qc are not linearly associated with increasing in SaO2. Reducing of Qc does not only modify Qec/Qc, it can also modify pulmonary shunt in reducing West zone 3. Therefore, a reducing of Qc does not lead to a proportional increasing of SO2.
Reply 1: We fully agree, that in cases where some lung function is preserved, a decrease in cardiac output might worsen pulmonary perfusion. In our original manuscript, we already stated, that we consider this concept to be only of use in cases of total lung failure. We put additional emphasis on the fact, that the concept is not valid, if some lung function is preserved.
Changes in Text 1: page 6, line 134-135: If there is some lung function left, this concept does not apply, since the potential influence of changes in cardiac output on the ventilation/perfusion mismatch have to be taken into account.(14)

Comment 2: Similarly, the influence of Qc change on Qec/Qc ratio under vv-ECMO depends on different parameters, especially ECMO configuration. Indeed, under inferior vena cava to right atrium route (i.e. fem-jug or fem-fem), in contrast with bicaval drainage (i.e. Avalon or VV-V), a structural recirculation leads beyond a significant value to a structural recirculation that makes a non-linear relationship between Qec and effective Qec (PMID: 33471364). Thus, the reducing of Qc may increase structural recirculation leading to a modest increasing of Qeff/Qc ratio, consequently a modest increasing of SaO2. To consider that DO2 A= DO2 B in reducing Qc is therefore particularly questionable or hazardous. However, I understand that some postulates must be established in a modelling.
Reply 2: We agree, that we did not discuss the topic of recirculation appropriately. We now included in our discussion, that recirculation especially in the femoro- jugular configuration may be high and a decrease in cardiac output may be dangerous and cited the recommended research. We further included, that our model only applies to a situation, where minimal recirculation can be achieved by use of a bi-caval dual lumen cannula and supported this with an appropriate reference.

Changes in Text 2: page 6, line 135- 139: Furthermore especially in the context of a femoro- jugular cannulation, recirculation might increase with a decrease in cardiac output(15). In this situation the use of beta blockers to reduce cardiac output may be hazardous. Our concept therefore only applies to a situation where minimal recirculation can be achieved as with a bi-caval dual lumen cannula. In this case recirculation may be negligible(16).

Comment 3: "PO2 in the veins draining a certain tissue (PvO2) is proportional to PO2 in the capillaries (PcapO2) with a constant factor k". This is in my opinion the greatest inaccuracy of this model. In a stable conditions, obviously PcapO2 = k PvO2. However, PcapO2 is firstly proportional with PaO2, following a partial pressure gradient. In their modelling, the authors should focus theirs analysis on PaO2 variations between situation A and situation B. PvO2 is the consequence of PcapO2 and not its cause. I suppose that the present modelling is wrong because PcapO2 are inadequate in presence of strong variation of PaO2. I strong suggest to the authors to establish PcapO2 using an equation integrating PaO2.
Reply 3: We fully agree that the use of PvO_2 may seem inappropriate and we failed to properly explain this.
The assumption, that $PcapO_2$ is proportional to PvO_2 is an assumption of the original model by Wagner. We consider this assumption to be in agreement with the current evidence on oxygen transport, as described in the Review Article that we included in our references (https://doi.org/10.1093/function/zqad013). We further studied the literature on experimental studies that directly examined the oxygen concentrations in the microcirculation. We think that the correlation of $PcapO_2$ with PvO_2 is supported by this review summarizing experimental studies on this topic. (See Fig 1 on Page 942 in DOI: 10.1152/physrev.00034.2002)
We do not think, that $PcapO_2$ is mainly determined by the oxygen content of the arterial blood. $PcapO_2$ is determined by the interplay of arterial oxygen content, cardiac output (i.e. DO2) and oxygen consumption. We therefore think that it is more appropriate to use $PvenO_2$ instead of PaO_2. PaO_2 and Q are the factors we want to modify with the use of the beta blocker. But if the oxygen consumption of the patient is constant, PvO_2 is mathematically determined by these factors (VO_2, Q and CaO_2).
We specified, that situations A and B are (as central assumptions of our model) are equal in regard to oxygen consumption. It is possible, that the oxygen consumption in the situation of a decreased cardiac output is actually lower, but we omitted this to simplify the discussion.
If oxygen consumption and oxygen delivery are constant, we can express this as follows (constant factors are omitted):

VO2 A = QA x (CaO2A-CvO2A) = VO2B = QB x (CaO2B-CvO2B)
This may be expressed as $\frac{Qa}{Qb} = \frac{CaO2B-CvO2B}{CaO2A-CvO2A}$

DO2 A = QA x CaO2A = DO2 B = QB x CaO2B
This may be expressed as $\frac{Qa}{Qb} = \frac{CaO2B}{CaO2A}$

Now we solve these two equations $\frac{Qa}{Qb} = \frac{CaO2B}{CaO2A} = \frac{CaO2B-CvO2B}{CaO2A-CvO2A} = \frac{CvO2B}{CvO2A}$

That means, that if only CO and CaO_2 are changed, with oxygen delivery and demand unchanged, the venous oxygen content is determined by these factors. We agree that this interaction is not intuitive for the ICU clinician, because usually with increase in CO CvO_2 rises. But in this specific situation, when DO2 is determined by the maximal ECMO flow, the ratio of CaO_2A and CaO_2B must be the same as the ratio of CvO_2A and CvO_2B. That also implies, that in the situation with higher Q and lower CaO_2, the absolute difference between CaO_2 and CvO_2 will be lower than in the low output situation, but the absolute value for CvO_2 will still be lower than in the low output situation.
Please allow us to illustrate our thought process with a specific example with simple (but unrealistic) numbers: Situation A: CO 7 liters, SaO_2 70%, SvO_2 35%. Situation B: CO 4,9 liters, SaO_2 100%. If we now consider that the oxygen consumption has not changed, SvO_2 in Situation B will be 50%. The difference between arterial and venous oxygen content is lower in the high output situation (as it is in physiologic conditions), but the absolute value for the venous oxygen content is still lower in the high output situation.
The venous oxygen content will only differ from the predicted value, if tissue hypoxia has occurred, which means, that the patients' situations are not equal any more. The situation with lower SvO_2 therefore puts the patient at higher risk for tissue hypoxia due to limitation on the diffusion level, but as long as hypoxia has not occurred, the VO_2 is the same.
We admit that we failed to explain this thought process properly, but we made the appropriate changes in the manuscript to explain this counter- intuitive situation.
Changes in Text 3: page 4, line 93- p 5 line 113:
We make some simplifying assumptions:

1. Situation A : High CO (QA) , low CaO_2 (CaO_2A), DO_2A = QA x CaO_2A; Situation B: Low CO (QB), higher CaO_2 (CaO_2B), DO_2B = QB x CaO_2B
2. Under the conditions of a CO that is significantly higher than the ECMO flow, a properly functioning oxygenator and minimal recirculation we consider $DO_2A = DO_2B$
3. Oxygen consumption remains constant in both situations VO2A = VO2B = QA x (CaO2A-CvO2A) = QB x (CaO2B – CvO2B)

If we put these assumptions together, we get the following relationship:

$$\frac{Qa}{Qb} = \frac{CaO2B}{CaO2A} = \frac{CaO2B-CvO2B}{CaO2A-CvO2A} = \frac{CvO2B}{CvO2A}$$

That implies, that in Situation A with higher Q and lower CaO_2, the absolute difference between CaO_2 and CvO_2 will be lower than in the low output situation, but the absolute value for CvO_2 will still be lower in situation A than in situation B.

Comment 4: Similarly, Wagner- diagram and all demonstrations are based on PvO2 which is not in my mind the central parameter of O2 Delivery. I would focus the comparison on DO2 and oxygen extraction (similar VO2) according to different conditions A/B.
Reply 4: As we illustrated in our reply 3, we think, that $PcapO_2$ is the central parameter for the diffusion process and this parameter may be expressed as $PvenO_2$ with a constant factor. Our central assumption is, that we want to compare two situations, that are equal in regard to the total amount of oxygen

delivered, which means that we assume VO_2 to be the same. We think that the situation with low $PcapO_2$ puts the patient at a higher risk for tissue hypoxia due to diffusion limitation. If the VO_2 decreases, then tissue hypoxia has already occurred. We think that we addressed this issue with the changes described above.
Changes in Text 4: no additional changes

Comment 5: In their mind, did authors integrate SvO2 (direct consequence of oxygen extraction) that is one of the main determinants of Spulm art O2 under vv-ECMO, and consequently SaO2 under vvECMO?? This determinant is major to consider when a reducing of Qc is envisaged. A reduced Qc induced indeed an increased O2 extraction and therefore a reduced SvO2. This feedback impacting SaO2 should be considered in this modelling. This is possible in determining a fixed Hb level.
Reply 5: We did not explicitly integrate SvO_2 in our model. As we explained in our response to Comment 3, if the oxygen consumption of the patient is constant and only CO and CaO_2 are changed the absolute value of SvO2 will be higher in the low output situation. The Difference between CaO_2 and CvO_2 will be higher in the low output situation, but under the conditions mentioned above (all oxygen provided by the ECMO, no residual lung function, DO_2 unchanged) the CvO_2 will still be higher in the low output situation. If we would consider the venous admixture of the deoxygenated blood that didn't pass the oxygenator, the oxygen content of the venous blood in situation B (low output, higher CaO_2 and consequently higher CvO2) would be favorable.
We included this aspect in our discussion.
Changes in Text 5: page 6, line 140- 141: If the effect of the admixture of deoxygenated blood is also taken into account, the PvO2 of the venous blood will also be higher in situation B as we calculated above.