Brief Report

Mechanisms of limitation of oxygen delivery during veno-venous extracorporal membrane oxygenation

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Abstract: Delivery of oxygen to the mitochondrium is a process involving multiple steps. We here present the integration of the mechanisms of oxygen delivery (DO_2) during veno-venous (V-V) extracorporal membrane oxygenation (ECMO) into a holistic physiological model. The final steps of oxygen transport in this model are the convective transport of oxygen bound to hemoglobin in the arterial blood and the diffusion to the mitochondrium from the microcirculation. Limitation of DO_2 may occur on both steps. In cases of severe respiratory failure without lung function, ECMO may provide the entire oxygen supply for the patients. If the cardiac output (CO) is significantly higher than the maximal ECMO flow, the addition of deoxygenated venous blood will lead to a low arterial oxygen saturation (SaO_2). In this situation the convective transport of oxygen is mostly limited by the maximal ECMO flow. If a bi-caval dual lumen cannula is used, the recirculation may be very low. Lowering the CO in this situation will increase the arterial SaO_2. An increased arterial SaO_2 may increase the oxygen transport to the mitochondrium by diffusion. The hypothesis derived from this model is that lowering the CO during V-V ECMO support in the situation described above might increase DO_2 to the tissues by improving oxygen diffusion.

Keywords: Veno-venous extracorporal membrane oxygenation (V-V ECMO); O_2 delivery; diffusion

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Ensuring adequate tissue oxygenation is a cornerstone of intensive care medicine. We here present a new integration of mechanisms of tissue oxygenation during veno-venous (V-V) extracorporal membrane oxygenation (ECMO) into a holistic physiologic model.

An integrated physiological model of tissue oxygenation describes oxygen delivery (DO_2) 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 DO_2 can be described as: $DO_2 = Q \times CaO_2$ [Q: cardiac output (CO); CaO_2: arterial oxygen content]. The main determinants of CaO_2 are Hb concentration and arterial oxygen saturation (SaO_2).

The oxygen consumption (VO_2) according to the Fick principle can be described as: $VO_2 = Q \times (CaO_2 - CvO_2)$ (CvO_2: venous oxygen content).

The DO_2 from the capillary to the mitochondrium with a certain diffusion capacity D can be described as: $VO_2 = D \times (PcapO_2 - PmitO_2)$ ($PcapO_2$: oxygen partial pressure in the capillaries; $PmitO_2$: 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

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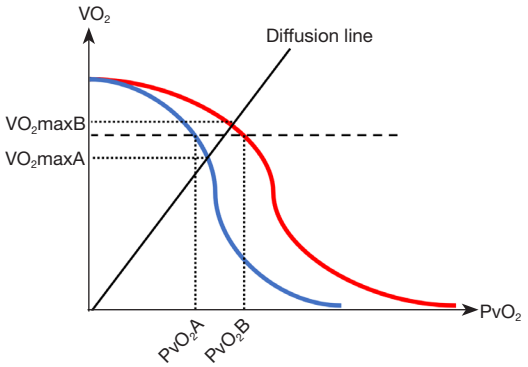

Figure 1 Wagner diagram of convective transport in Situation A (blue line) and Situation B (red line). Dotted vertical lines: PvO_2 at a given VO_2 represented by the broken line. Dotted horizontal lines: VO_2max in Situation A and Situation B. PvO_2, venous oxygen partial pressure; VO_2, oxygen consumption; VO_2max, maximal VO_2.

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 Hb following the sigmoid oxygen dissociation curve, the connective and diffusive DO_2 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 DO_2 (5).

Patients with severe respiratory failure may experience a total loss of lung function. In these cases, V-V ECMO may provide the entire oxygen supply for the patients. If the Hb is considered constant, the CaO_2 is determined by the maximal ECMO flow, because we consider the ECMO oxygenator to be capable of fully oxygenating all blood passing through the oxygenator.

In a subset of patients, a high CO that is significantly higher than the maximal achievable effective ECMO flow, will lead to a significant addition of deoxygenated venous blood, thus lowering the SaO_2. There is controversy, if the addition of beta-blockers with the intention of lowering the CO and thus increasing the SaO_2 is beneficial, because the total amount of oxygen delivered by ECMO is not changed (7).

To introduce our integrated model of tissue oxygenation during V-V ECMO in cases of total lung failure, we analyze two situations (Situation A and Situation B). We consider these situations to be completely equal regarding ECMO flow and all physiologic parameters and to differ only in regard to CO and SaO_2

We make some simplifying assumptions:

(I) 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), $DO_2B = QB \times CaO_2B$

(II) Under the conditions of a CO that is significantly higher than the ECMO flow, a properly functioning oxygenator and minimal recirculation we consider $DO_2A = DO_2B$

(III) VO_2 remains constant and equal in both situations $VO_2A = VO_2B = QA \times (CaO_2A - CvO_2A) = QB \times (CaO_2B - CvO_2B)$.

If we put these assumptions together, we get the following relationship: $QA/QB = CaO_2B/CaO_2A = (CaO_2B - CvO_2B)/(CaO_2A - CvO_2A) = CvO_2B/CvO_2A$.

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.

With these underlying assumptions we can generate a Wagner diagram depicting Situation A and Situation B (*Figure 1*). The intersections of the diffusion line with the curves of the convective transport are the values for maximal VO_2 (VO_2max).

As it can be seen on the diagram, we consider the convective maximal DO_2 to be identical in both situations. 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.

If we now introduce the diffusion capacity in our model, we see that the VO_2max on the diffusion step is higher in Situation B, because the concentration gradient of O_2 between the capillary and the mitochondrium is higher.

Since a limitation on the diffusion step has been described in past research (8,9), we consider it to be an important component of a holistic concept of DO_2 into the tissues.

While values for arterial oxygen partial pressure (PaO_2) around 60 mmHg have been considered safe in past clinical trials (HOT-ICU, ICU-ROX), the $LOCO_2$ trial with a target of 55–70 mmHg in the conservative oxygen group was stopped early because of an increased number in mesenterial ischemia (10-12).

Our hypothesis is, that in PaO_2 values below the lower threshold in the past trials, a diffusion limitation might lead to tissue hypoxia in patients with low CaO_2 values despite an identical convective DO_2. Diffusion limitation

as the limiting factor of DO_2 has previously been described (8,13,14). We therefore suggest, that the use of medications to decrease the CO in situations of total lung failure and ECMO support might decrease the risk of tissue hypoxia by accounting for the risk of a limitation on the diffusion step. The use of a short acting medication like esmolol is preferable in this situation in cases where adverse events are observed.

If there is some lung function left, this concept does not apply, since the potential influence of changes in CO on the ventilation/perfusion mismatch have to be taken into account (15). Furthermore, especially in the context of a femoro-jugular cannulation, recirculation might increase with a decrease in CO (16). In this situation the use of beta-blockers to reduce CO 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 (17). If the effect of the admixture of deoxygenated blood is also taken into account, the PvO_2 of the venous blood will also be higher in Situation B as we calculated above.

While a previously discussed mathematical model suggests, that the convective DO_2 is improved in the situation of increased CO and reduced SaO_2, this does not take into account the following steps of tissue oxygenation (7). Furthermore, a decrease in CO might worsen perfusion on the microvascular level. To our knowledge, there is currently no established cut-off for CO and CaO_2 to decide when lowering CO and thus increasing diffusion is beneficial.

There are multiple possible options to solve this question, including data mining of hemodynamic and blood gas data from patients treated with V-V ECMO, mathematical modelling of tissue perfusion and diffusion or models using animal tissue for direct testing.

Further data is needed to evaluate whether the effects predicted by this model have a clinically meaningful effect.

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Footnote

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