Critical Care

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Early hyperoxia and 28-day mortality in patients on venoarterial ECMO support for refractory cardiogenic shock: discussion about potential confounding factors

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To the Editor,

We would like to commend Moussa et al. for their work recently published in Critical Care [1] in which they demonstrated an association and a dose–response between early hyperoxemia and 28-day mortality in patients with refractory cardiogenic shock supported by veno-arterial extracorporeal membrane oxygenation (VA-ECMO). While several studies have previously reported such association in the setting of extracorporeal cardiopulmonary resuscitation, previous studies enrolling patients with refractory cardiogenic shock have reported conflicting results [2].

Although we think, as the authors, that the harmful effect of hyperoxemia in these very sick patients exposed to ischemia and reperfusion is probable, we would like to discuss some possible confounding factors.

First, the association between right arm hyperoxemia and prognosis reported in observational studies might be impacted by the native cardiac function. Indeed, during femoro-femoral VA-ECMO, the right arm P_aO_2 is determined by both S_vO_2, hemoglobin concentration, native lung function, inspired oxygen fraction on ventilator (F_IO_2), positive end expiratory pressure, sweep gas oxygen fraction (F_SO_2), and the balance between native cardiac function and ECMO blood flow. The later determines the mixing zone location, *i.e.*, the zone in the aorta where the blood ejected from the heart and oxygenated by the lungs meets the blood ejected and oxygenated by the ECMO [2]. Because of the oxygenator's performance, postoxygenator oxygen partial pressure ($P_{POST}O_2$) can rise to 500 mmHg. Then, hyperoxemic patients might be those for whom right arm P_aO_2 is mainly determined by the ECMO when the mixing zone is in the aortic arch close to the brachiocephalic trunk. Such situation might occur in case of high ECMO blood flow and severe cardiac failure, which could lead per se to a poor prognosis.

To explore this possibility, the authors have tested the interaction between ECMO blood flow and right arm P_aO_2 on admission. Although they did not find any association, we cannot rule out that mean daily peak P_aO_2, absolute peak P_aO_2, and overall mean P_aO_2 could be associated with ECMO blood flow. It could be also of interest to test the association between right arm P_aO_2 and surrogates of native cardiac function, such as pulse pressure or end tidal CO_2 [3].

Another way to support the causality link between hyperoxemia and poor prognosis is to demonstrate that exposition to oxygen is different between survivors and non-survivors. In Table 2, it is unclear if the "F_IO_2" corresponds to the inspired oxygen fraction on the ventilator, or to the F_SO_2 set on the ECMO. It could be of interest to precise both F_IO_2 and F_SO_2. If "F_IO_2" actually corresponds to F_SO_2, we can hypothesize that $P_{POST}O_2$ was

This comment refers to the article available online at https://doi.org/10.1186/s13054-022-04133-7.

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higher in non-survivors than in survivors, which potentially has resulted in more reperfusion injury of intra-abdominal organs mediated by radical oxygen species [4].

Finally, the number of arterial blood gas (ABG) analysis performed during the 48 first hours of VA-ECMO support might be an interesting data to show to ensure that different overall mean P_aO_2 reflect different oxygen exposure. Indeed, overall mean P_aO_2 is mathematically linked to the number of ABG sampled. If several ABG analyses are performed during a short period of hyperoxemia, overall mean P_aO_2 could overestimate oxygen exposure. Assuming that the most severe patients have more frequent ABG analysis, we cannot exclude that overall mean P_aO_2 could overestimate oxygen exposure in most severe patients. Then, it could be of interest to determine the relation between 28-day mortality and time-weighted P_aO_2 [5], a metric of arterial oxygenation which better reflects oxygen exposure than overall mean P_aO_2.

Beyond these points of discussion, Moussa et al. have to be congratulated for their work which adds rationale for the two ongoing randomized trials on oxygen management during VA-ECMO support (BLENDER NCT03841084, and ECMOXY NCT04990349).

Response

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Dear Dr Winiszewski,

We would like to thank Dr Winiszewski and colleagues for their comments that raises one of the major question regarding the management of peripheral veno-arterial ECMO (VA-ECMO)—"What are the determinants of arterial oxygenation in patients receiving VA-ECMO support?". Numerous studies have attempted to answer this question, but data are limited for VA-ECMO patients and are even more limited when only patients in cardiogenic shock are considered (excluding eCPR). Retrograde arterial blood flow and mixed blood flow zone phenomena exist only in the VA-ECMO settings, which do not allow extrapolation of data from VV to VA-ECMO.

Andrei and colleagues [6] recently provided the interesting observation that the main determinants of PaO_2 measured at the right arm level are the blood flow delivered by the VA-ECMO and the sweep gas oxygen fraction. None of the ventilator parameters (FiO_2, respiratory rate) were associated with right arm PaO_2. Furthermore, this study demonstrated that during the initial phase of VA-ECMO support, the impact of the native heart function could be neglected and was not related to PaO_2. Indeed, the participation of the native cardiac function on the PaO_2 is modulated by the level of VA-ECMO assistance. The greater the level of VA-ECMO support, the lower the contribution of the native cardiac function. However, we usually observe during the initial phase of refractory cardiogenic shock a collapsed native heart function and a high level of VA-ECMO support (i.e., high blood flow), which suppresses the influence of the native heart on PaO_2. This may also explain why pulse pressure, which is largely determined by the native heart function, is not associated with right arm PaO_2. Thus, at the start of VA-ECMO support, an elevated right arm PaO_2 may often reflect hyperoxemia throughout the body. Because our study focused on the early period of VA-ECMO support, we believe that we have avoided these confounding factors.

We agree that the time-weighted PaO_2 may better reflect the time of exposure to hyperoxemia than two time points over a 24-h period, but this remain difficult to use in clinical practice. All patients underwent arterial blood gases according to the local centers' "standard of care", so that we can assume that a quite similar number of PaO_2 measurements were obtained in each patient.

This method is far from perfect, but it is clinically relevant and close to what is reported in previous studies evaluating hyperoxemia [7].

In summary, despite these limitations that were already discussed [8] and based on the above arguments, we believe that hyperoxemia is associated with a higher risk of 28-days mortality. Hopefully, further randomized clinical trials (BLENDER NCT03841084 and ECMOXY NCT04990349) will be able to answer this question.

Author contributions
HW, GP, GC, MDM, CB and OAA wrote the manuscript. All authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no conflict of interest.

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Received: 10 September 2022 Accepted: 14 September 2022
Published online: 17 October 2022

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