

As concern the second point of your letter, we completely agree with you regarding the need of further prospective validation of our work. Although limited by retrospective design, the need for a standardization of sign and symptoms was clear to us, and we analyzed our clinical records wisely to achieve that. This point was facilitated by our single center design, since our emergency physician staff, and neuro-radiologist staff, was the same in the whole period observed into the study. However our study limitations remains very clear to us, and this point is underlined at the end of the manuscript where we state: “*Limitation of this study include the single center design, and the reduced sample observed. An independent validation of the score is obviously necessary, possibly by prospective controlled trials, prior to consider it in common clinical practice*”.

I hope that further authors could contribute to better define these issues that are of sure interest for emergency physicians and could surely reduce unnecessary use of CT scan in the ED.

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“The authors reply” Prehospital Ventilation and Oxygen strategy in septic patients



Dear Editor,

We thank Karim et al. [1] for their interest and relevant comments about our article [2].

First, as they underlined in their letter, our work suggests an association between hyperoxemia in patients with septic shock subjected to prehospital mechanical ventilation and mortality at 28 days upon intensive care unit admission (ICU) [2]. We agree that these observations raise an important issue, even considered as a controversial “hot topic”.

Interestingly, many teams are currently evaluating the benefit/risk balance between only strictly correcting hypoxemia, versus applying a more liberal oxygen strategy in patients presenting with life-threatening critically ill conditions [3]. The use of a conservative oxygen strategy to avoid patient exposure to unnecessary hyperoxemia is close to be admitted by many physicians [4]. A clinical trial, prematurely stopped, simultaneously evaluated hyperoxia versus normoxia associated with hypertonic versus isotonic saline infusion in a 2 × 2 factorial design in septic patients. The authors reported an increased mortality rate in the hyperoxia arm (NCT01722422) [5]. A randomized study is currently ongoing to assess short- and long-term effects of two different arterial partial pressures of oxygen (PaO₂) targets for ICU patients presenting with systemic inflammatory response syndrome (105–135 mmHg versus 60–90 mmHg, O₂-ICU study, NCT02321072). This study might provide

answers as to whether or not hyperoxemia may have beneficial or deleterious effects in septic patients.

Hyperoxemia and molecular downstream mechanisms are time-dependent. Most data gathered in the ICU have focused on patient's outcomes associated with relatively prolonged hyperoxemia, from the first 24–72 h of ICU stay to the entire period of mechanical ventilation [6]. In the first 24 h after ICU admission, deleterious effects of hyperoxemia were reported on mortality [7]. Data from animal studies reported negative effects of hyperoxemia after only a few hours of exposure, leading to changes in inflammation and pulmonary mechanics [8, 9]. Overstimulation of mitochondrial functioning increases the release of cytochrome c, which induces the activation of apoptotic pathways. In parallel, hyperoxemia depletes cellular ATP, and increases the production of reactive oxygen species (ROS) leading to oxidative damage. ROS produce mitochondrial damage impacting ATP production [10]. Nevertheless, the effects of hyperoxemia and their time to onset in the prehospital setting remain unclear. A recent work evaluating relatively brief exposure (3.5–7.5 h) to hyperoxemia in the emerging department prior to ICU admission in critically ill patients showed negative clinical outcomes [11].

The exact exposure time to hyperoxemia was not precisely given in our work [2]. However, our patients were approximately exposed to high oxygen levels in the prehospital setting of average of 99 ± 39 min. In our study, patients were intubated and mechanically ventilated because they needed to, as they presented with acute respiratory failure, so that the use of non-invasive ventilation was not appropriate in this context.

The absence of accurate monitoring of partial arterial pressure of oxygen (PaO₂) in the prehospital setting is inherent to the specificities of this working environment. This situation is unfortunately frequent in the prehospital setting, where liberal oxygen therapy is generally performed. Modification of the fraction of oxygen concentrations (FiO₂) induces changes in the PaO₂ in time interval of 30 to 60 min approximately. Consequently, good clinical practices in the prehospital setting are harder to evaluate compared to inside the hospital, since precise monitoring of gas exchanges is less accessible.

However, our study described real clinical practices in the prehospital setting and consequently emphasizes the need for more accurate data on prehospital patients, and the need for guidelines on ventilator settings, especially regarding FiO₂.

Secondly, we included all patients above 18 years with septic shock criteria according to the surviving sepsis campaign definition [12], and subjected to assisted-mechanical ventilation before hospital admission [2]. Our patients did not have conditions associated with ischemia/reperfusion injury, such as post-cardiac arrest or stroke.

Thirdly, in emergency situations, patient's medical history should not affect the patient's management. The priority of care is driven by neurological, respiratory and hemodynamic failures. The SOFA score was not different between our two groups ($p = 0.12$). Statistical analysis was performed using propensity scoring ensuring adjustment on confounding factors. A Student t -test is not an adequate test for a small population and data were not distributed according to a normal distribution. Wilcoxon test might be used for non-gaussian distribution but is not appropriate in this type of studies. Using propensity score analysis including SOFA score, pre-hospital duration, lactate, and pre-hospital fluid volume expansion, association with mortality at 28 days only remained significant for a PaO₂ > 150 mm Hg ($p = 0.02$, OR [CI95] = 1.59 [1.20–2.10]). Deceased patients had higher PaO₂/FiO₂ ratio, meaning that deceased patients were more frequently exposed to hyperoxemia. This observation is an agreement with the conclusion of our work.

Hyperoxemia deleterious effects appear early in the management of mechanically ventilated patients. Hyperoxemia is frequent in patients subjected to mechanical ventilation due to acute respiratory failure in emergency conditions. Therefore, FiO₂ should be set with awareness as fast as possible even in the prehospital setting, to avoid over exposure

to high levels of oxygen. Precise monitoring of gas exchange is not yet easily feasible in the prehospital setting. As an alternative, pulse oximetry (SpO₂) can help to monitor gas exchanges until hospital arrival. The trend is therefore moving toward a more conservative approach regarding oxygenation management. The aim is to maintain a SpO₂ target at 95–97%, although the optimal PaO₂ level has not yet been defined [13]. Nevertheless, it is important to keep in mind that SpO₂ target might also change during the course of patient's management, and consecutively re-evaluation appears to be the rule.

Finally, we thank Karim et al. [1] for their letter. Indeed, communication between research teams is a key tool to improve our clinical practices. As clearly summarized, none of the potential methods toward a feasible monitoring of gas exchange are perfect when it comes to the prehospital field. Further well-designed randomized controlled trials in critically ill patients with septic shock may help to provide some definitive answers to these questions and uncover the precise characteristics of the unwanted company.

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Pre-hospital invasive ventilation in patients with septic shock: Is hyperoxemia an unwanted company?



To the Editor,

Hyperoxemia presents a dangerous association with short outcome, by complex pathways [1]. In this line, we read with great interest the article of Jouffroy R et al. suggesting the association between hyperoxemia in septic shock patients who needed ventilator support in the prehospital setting and short term mortality [2]. The study reiterates the fact that hyperoxia might be dangerous for critically ill patients [1, 3], and also suggests that a PaO₂ between 100 and 150 mm Hg might be harmful in these patients. However, in our opinion, the authors open a hot controversial topic in their study which needs some more information of key determinants.

Firstly, hyperoxemia and its complication are associated with time effect. Although the retrospective studies show a deleterious effect of short term hyperoxemia, this is particularly pronounced during long-term administration, i.e., beyond 12–24 h [4]. Time period of hyperoxemia is unknown from the study. Moreover, the ventilator management was left up to the discretion of emergency physician without any protocol driven strategy, which itself has inherent bias which can affect the fraction of oxygen concentrations (FiO₂) used and arterial partial pressure of oxygen (PaO₂). The information on the use of noninvasive ventilation and the FiO₂ also becomes very pertinent.

Secondly, the data of Jouffroy R, et al. are hypothesis generating for the time being and it would be useful for the scientific community to know the information regarding how many patients had conditions associated with ischemia/reperfusion injury, such as post-cardiac arrest or stroke etc. as they all determine the short and short and long term outcome as well as relations with hyperoxemia [5].

Thirdly, the disease severity at the admission/starting of medical care is also important. Although the data from table 1 of the study with context to blood pressure, need of norepinephrine doses and number of patients required norepinephrine supports were not different; the patients were not similar in terms of severity of diseases. The patients who survived were having significantly lower sequential organ failure assessment score; p 0.007, and higher PaO₂/FiO₂; p 0.01 (two tailed p from t-test analyzed by Graphpad). This indicates that the patients compared were not similar rather the patients who had hyperoxemia were more severely diseased. Therefore, the conclusion of the study will not be much more acceptable after ruling out the contributing factors for patients' inherent conditions at the time of admission, which can contribute to mortality.

Finally, monitoring gas exchange by pulse oximetry and capnography is easier and more general approach and even well feasible in patients with septic shock. Although pulse oximetry cannot detect hyperoxemia by exact values, it can give an idea of hyperoxemia when SpO₂ is >95% [6]. The arterial blood gases (ABG)

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Abbreviations: PaO₂, arterial partial pressure of oxygen; FiO₂, fraction of oxygen concentration; ABG, arterial blood gas.