Original Contribution

Prognosis value of partial arterial oxygen pressure in patients with septic shock subjected to pre-hospital invasive ventilation

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ABSTRACT

Objective: Mechanical ventilation can help improve the prognosis of septic shock. While adequate delivery of oxygen to the tissue is crucial, hyperoxemia may be deleterious. Invasive out-of-hospital ventilation is often promptly performed in life-threatening emergencies. We propose to determine whether the arterial oxygen pressure (PaO_2) at the intensive care unit (ICU) admission is associated with mortality in patients with septic shock subjected to pre-hospital mechanical ventilation.
Methods: We performed a monocentric retrospective observational study on 77 patients. PaO_2 was measured at ICU admission. The primary outcome was mortality at day 28 (D28).
Results: Forty-nine (64%) patients were included. The mean PaO_2 at ICU admission was 153 ± 77 and 202 ± 82 mm Hg for alive and deceased patients respectively. Mortality concerned 18% of patients for $PaO_2 < 100$, 25% for $100 < PaO_2 < 150$ and 57% for a $PaO_2 > 150$ mm Hg. PaO_2 was significantly associated with mortality at D28 ($p = 0.04$). Using propensity score analysis including SOFA score, pre-hospital duration, lactate, and prehospital fluid volume expansion, association with mortality at D28 only remained for $PaO_2 > 150$ mm Hg ($p = 0.02$, OR [CI95] = 1.59 [1.20–2.10]).
Conclusions: In this study, we report a significant association between hyperoxemia at ICU admission and mortality in patients with septic shock subjected to pre-hospital invasive mechanical ventilation. The early adjustment of the PaO_2 should be considered for these patients to avoid the toxic effects of hyperoxemia. However, blood gas analysis is hard to get in a prehospital setting. Consequently, alternative and feasible measures are needed, such as pulse oximetry, to improve the management of pre-hospital invasive ventilation.

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1. Introduction

Sepsis is a major public health problem with an estimated incidence of 300 per 100,000 inhabitants in the US [1,2]. Morbidity and mortality related to sepsis are well documented in the intensive care unit (ICU) [3-5]. Despite an improvement in the prognosis observed during the last decades [3,6], the mortality rate remains high, reaching 30% at day 28 (D28) [1,6-8]. The outcome of septic patients relies on early identification of patients at risk and on rapid implementation of appropriate treatments [7,9].

In sepsis, acute respiratory distress syndrome is frequently encountered. Consequently, early identification of septic shock requiring invasive ventilation leads to rapid implementation of respiratory support to help improve the prognosis [10]. While adequate delivery of oxygen to tissue is crucial, hyperoxemia may have disastrous consequences

[11-13]. Oxygen administration during invasive ventilation often exposes the patient to hyperoxemia due to suboptimal practice [14]. In the ICU, 15.6% of hospitalized patients are subjected to hyperoxemia on the first intubation day [15]. Hyperoxemia caused by invasive ventilation results in increased ventilator-associated pneumonia [16,17]. Deleterious effects of hyperoxemia on survival have been reported, especially after cardiac arrest and traumatic brain injury [11-13,18]. Actually in critically ill patients, uncontrolled delivery of oxygen during reperfusion upon ischemia is associated with poor outcomes [12,18]. In the case of sepsis, hyperoxemia frequently occurs due to the physician's first priority to prevent and treat hypoxia. The association between mortality and oxygen arterial partial pressure (PaO_2) in septic patients was reported to follow a quadratic form, with both low and high PaO_2 associated with high mortality risk, along with a link between PaO_2 and the severity of sepsis [19]. Guidelines for the ventilatory management of patients with septic shock recently published a target for PaO_2 over 60 mm Hg and/or for SpO_2 between 88 and 95% [20]. However, no recommendations were proposed concerning the upper limit of PaO_2.

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The present study aimed to determine whether an association between hyperoxemia at ICU admission defined by PaO_2 and mortality at day 28 (D28) exist in septic shock subjected to pre-hospital invasive ventilation.

2. Methods

2.1. Study design

In France, out-of-hospital emergencies are managed by the French pre-hospital emergency service called "Service d'Aide Médicale d'Urgence (SAMU 15)". The SAMU hospital-based team, composed of switchboard operators and physicians, is reached calling the national access telephone number 15. Over the phone, the SAMU determine the appropriate level of care to dispatch to the scene, based on the patient's medical history and symptoms related by the patient and/or relatives. For life-threatening emergencies, i.e. cardiac arrest, septic shock or severe trauma, the "Service Mobile d'Urgence et de Réanimation" (SMUR), is dispatched to the scene. The SMUR is a mobile intensive care unit (MICU), composed of a driver, a nurse and an emergency physician [21]. In a context of neurological and/or respiratory failure, invasive ventilation can be necessary and performed by the SMUR prior to hospital admission [22].

All consecutive patients admitted to the ICU of Necker Hospital, between January 2012 and January 2015, who received pre-hospital medical care, were retrospectively analyzed. Among these, all patients above 18 years with septic shock criteria according to the surviving sepsis campaign definition [23], and subjected to assisted-mechanical ventilation before hospital admission were included. Patients younger than 18 years, pregnant women and patients who did not require invasive ventilation in the pre-hospital setting were not included in the study.

Patients were ventilated in the prehospital setting using a portable ventilator (Elisée 250™ by ResMed©). Pre-hospital assisted-mechanical ventilation was motivated by acute respiratory failure and/or comatose status and left at the physician's discretion. Actually, in France, no guidelines exist yet for the management of prehospital mechanical ventilator and to set ventilator parameters. PaO_2 level was measured directly at ICU admission from blood sample taken from intra-arterial access. Blood sample was immediately processed on a standard blood gas analyzer (ABL 800 FLEX Radiometer©). Calibration and quality control were performed on daily basis according to the manufacturer's instructions.

The primary outcome was mortality at D28.

Considering the retrospective character of the study, no committee approval was required.

2.2. Data collection and statistical analysis

Data were collected by a single investigator and extracted from MICU and ICU medicals reports. Covariates were defined prior to data collection and included: patients' demographic characteristics (age, weight, size, and gender), immunosuppression status, vital signs (mean blood pressure, diastolic and systolic blood pressure, heart rate, pulse oximetry, respiratory rate, and temperature), duration of pre-hospital care, and length of stay in the ICU. The Sequential Organ Failure Assessment (SOFA) score [24] was established for each patient 24 h upon ICU admission.

First, a univariate analysis, to evaluate the relationship between mortality and all the covariates, was performed. Then, a propensity score analysis including SOFA score, pre-hospital duration, lactate, and pre-hospital fluid volume expansion was used.

Thereafter, as described by Girardis et al. [25], the continuous variable PaO_2 was categorized in 3 levels: $70 < PaO_2 < 100$ mm Hg, $100 < PaO_2 < 150$ mm Hg and $PaO_2 > 150$ mm Hg, to study the relationship between mortality and PaO_2 levels.

Comparison between the PaO_2 levels was performed using the Chi^2-test.

Results are expressed as mean with standard deviation for quantitative parameters and, as absolute value and percentage for qualitative parameters. Results are given as Odds Ratio (OR) with 95% confidence interval (CI95).

Data analyses were performed using R© version 3.2.3.

3. Results

Between January 2012 and January 2015, 77 patients with septic shock received pre-hospital medical care and were admitted to the ICU. Among them, 28 patients (36%) did not require mechanical ventilation prior to ICU admission and were thus excluded from the analysis. Finally, 49 patients (64%) subjected to invasive out-of-hospital ventilation were considered (Fig. 1). All mechanically ventilated patients required optimal respiratory support in the context of acute respiratory distress caused either by the severity of the pulmonary infection or as a manifestation of septic shock.

Table 1 describes the populations' demographic and clinical characteristics. Twenty-eight patients (59%) were male and the mean age was 65 ± 16 years. Origin of septic shock was mainly pulmonary (71%) (Table 2). The mean SOFA score at 24 h upon ICU admission was 11 ± 3 (Table 1).

The mean length of stay in the ICU was of 13 ± 14 days (Table 1). Mortality rate at D28 reached 39%. All deaths were caused by multiple organ failure.

No significant difference was observed in the duration of pre-hospital mechanical ventilation between alive and deceased patients (100 ± 38 min vs 97 ± 37 min respectively, $p = 0.74$; Table 1). Mean PaO_2 at ICU admission of alive and deceased patients was 153 ± 77 mm Hg and 202 ± 82 mm Hg respectively (Table 1). A trend towards increasing mortality rate with increasing PaO_2 levels was observed (Fig. 2). A significant different was found between mortality rate observed for $PaO_2 < 100$ mm Hg and $100 < PaO_2 < 150$ mm Hg ($p = 0.03$) and for $100 < PaO_2 < 150$ mm Hg and $PaO_2 > 150$ mm Hg ($p = 0.02$) (Fig. 2).

In the univariate analysis, a significant association with mortality was found for PaO_2 ($p = 0.04$, OR [CI95] = 1.01 [1.01–1.02]) (Table 3).

Using propensity score analysis including SOFA score, pre-hospital duration, lactate, and pre-hospital fluid volume expansion, association with mortality at D28 only remained significant for $PaO_2 > 150$ mm Hg ($p = 0.02$, OR [CI95] = 1.59 [1.20–2.10]).
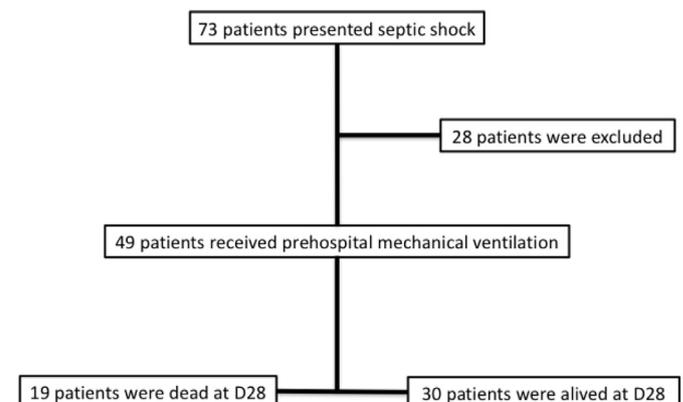

Fig. 1. Flow Chart of the study.

Table 1

Demographic, clinical and biological characteristics of patients with septic shock subjected to pre-hospital invasive ventilation. Quantitative variables are expressed as mean ± standard deviation. Qualitative variables are expressed as absolute values and percentages.

	Alive patients at D28 (n = 30)	Deceased patients at D28 (n = 19)	Overall patients (n = 49)
Age (years)	63 ± 16	65 ± 18	65 ± 16
Weight (kg)	67 ± 17	69 ± 18	68 ± 16
Size (cm)	169 ± 9	169 ± 13	169 ± 10
Male	15 (55%)	11 (61%)	26 (58%)
Immunosuppression	17 (63%)	14 (78%)	31 (69%)
Mean blood pressure (mm Hg)	73 ± 24	71 ± 13	72 ± 20
Systolic blood pressure (mm Hg)	100 ± 27	96 ± 17	99 ± 24
Diastolic blood pressure (mm Hg)	61 ± 15	60 ± 21	60 ± 19
Heart rate (beats/min)	123 ± 26	117 ± 23	121 ± 24
Pulse oximetry (%)	84 ± 11	83 ± 13	83 ± 11
Respiratory rate (moves/min)	28 ± 9	32 ± 8	30 ± 9
Temperature (°C)	38.5 ± 1.6	38.9 ± 1.4	38.1 ± 2.1
Duration of pre hospital care (min)	100 ± 38	97 ± 37	99 ± 39
Length of stay in the ICU (days)	15 ± 17	11 ± 12	14 ± 15
SOFA	10 ± 2	12 ± 3	11 ± 3
PaO_2 (mm Hg)	153 ± 77	202 ± 82	170 ± 82
PaO_2/FiO_2	245 ± 81	180 ± 103	205 ± 99
Fluid volume expansion (ml/kg)	17 ± 13	13 ± 13	15 ± 13
Lactate level at admission (mmol/l)	5.3 ± 2.2	6.5 ± 2.9	5.8 ± 2.5
Number of patients with norepinephrine	16 (53%)	14 (74%)	30 (61%)
Dose of norepinephrine (μg/kg/min)	0.92 ± 1.04	1.40 ± 1.10	1.14 ± 1.10

Fig. 2. Proportion of patients in the predefined categories of PaO_2 level at ICU admission.
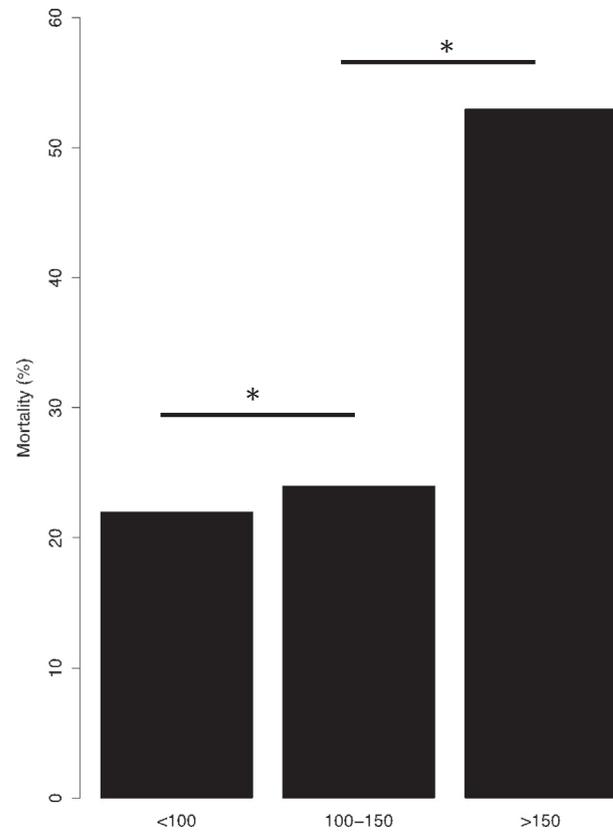
4. Discussion

In this study, we observed that elevated PaO_2 at ICU admission of septic patients subjected to invasive pre-hospital mechanical ventilation was associated with increased mortality at day 28.

Out-of-hospital emergencies, such as cardiac arrest or septic shock, often require early pre-hospital mechanical invasive ventilation due to acute respiratory distress. In this context, clear guidelines on ventilatory support, especially on oxygen management, are lacking. A PaO_2 > 60 mm Hg and/or an SpO_2 between 88 and 95% have recently been suggested for optimum oxygen therapy [19]. Durlinger et al. described an increase in arterial hyperoxemia when SpO_2 is >95% [26]. However, the optimum range of PaO_2 and SpO_2 remains controversial with the lack of consensus upper target limit that define hyperoxemia in patients with septic shock. In sepsis, effects of hyperoxemia are still controversial [27-32]. Actually, the goal of early oxygen therapy is to achieve adequate delivery of oxygen to the tissue to correct and treat hypoxia. However, adequate oxygen therapy to prevent potential hyperoxemia is not yet a part of our clinical practice, despite recent discoveries of harmful effects of oxygen. Significant association between hyperoxemia and poor outcome, such as neurological failure and mortality, was extensively observed in patients with cardiac arrest [11-13]. In a recent study, Elmer and colleagues considered severe hyperoxemia as a PaO_2

> 300 mm Hg in patients with cardiac arrest responsible for increased mortality rate [33]. A similar cut-off was reported to be deleterious in septic patients [19]. The adverse effects of hyperoxemia are underestimated, as on the first day in ICU, 15.6% patients are subjected to hyperoxemia [15]. The oxygen paradox described in the ischemia-reperfusion syndrome in the context of cardiac arrest resuscitation shows pathophysiological similarities with sepsis [34]. Briefly, high

Table 2

Origin of sepsis of patients admitted to the ICU subjected to pre-hospital invasive ventilation. Data are expressed as absolute values with their percentages.

Site of infection	Number of patients (%)
Pulmonary	32 (71%)
Urinary	7 (16%)
Meningeal	2 (4%)
Prostatic	1 (2%)
Digestive	1 (2%)
Invasive medical device	1 (2%)
Undefined	1 (2%)

Table 3

Univariate analysis of variables predictive of mortality at D28 in patients with septic shock admitted to the ICU subjected to pre-hospital invasive mechanical ventilation. Data are presented as p values and Odds Ratio (OR) with a 95% confidence interval (95CI).

Variables	Univariate analysis	
	OR (95CI)	p value
Age (years)	1.02 [0.98–1.06]	0.43
Weight (kg)	1.01 [0.97–1.04]	0.98
Height (cm)	0.99 [0.93–1.05]	0.71
Male	1.31 [0.41–4.40]	0.65
Immunosuppression	2.17 [0.60–9.10]	0.25
Mean blood pressure (mm Hg)	1.01 [0.97–1.03]	0.82
Systolic blood pressure (mm Hg)	0.99 [0.97–1.02]	0.60
Diastolic blood pressure (mm Hg)	1.01 [0.97–1.04]	0.78
Heart rate (beats/min)	0.99 [0.97–1.02]	0.62
Pulse oximetry (%)	0.99 [0.94–1.05]	0.81
Respiratory rate (moves/min)	1.06 [0.99–1.14]	0.13
Duration of pre-hospital care (min)	1.01 [0.89–1.12]	0.24
Length of stay into ICU (days)	0.97 [0.92–1.02]	0.26
Lactate level at ICU admission	1.20 [0.96–1.57]	0.13
Dose of norepinephrine (μg/kg/min)	1.40 [0.70–2.98]	0.35
Fluid volume expansion indexed on body weight (ml/kg)	0.97 [0.92–1.02]	0.32
SOFA score at 24 h	1.18 [0.96–1.49]	0.12
PaO_2 (mm Hg)	1.01 [1.01–1.02]	0.04*

production of reactive oxygen species occurs in cardiac fibroblasts after exposure to hyperoxemia. Thereafter, the generated reactive oxygen species are released by mitochondria, alter the protein membrane transport and induce membrane lipid peroxidation damaging the endothelium [34,35].

Several limitations can be mentioned in the work presented herein. First, this study is a single center with a small sample size. Second, sorting bias might exist due to the sampling method. On the one hand, data were retrieved from MICU and ICU reports. On the other hand, data abstraction was not performed using a standardized template. Third, PaO_2 levels were collected at ICU admission and pre-hospital PaO_2 was not retrieved. Consequently, the duration of hyperoxemia cannot be determined. Therefore, it is impossible to know whether at some point the PaO_2 was optimum and whether oxygen is related to dose and/or duration of hyperoxemia. Anyhow, data on the impact of the exposure duration to hyperoxemia in adult are scarce. A recent work showed a linear and positive relationship between time spent in hyperoxemia and mortality in the ICU [36]. Interestingly, harmful effects caused by conventional versus restrictive oxygen therapy, occur after longer exposure periods than the mean duration of pre-hospital herein. Girardis et al. [25] reported a decrease of ICU mortality in patients hospitalized for at least 72 h when a protocol for conservative oxygen therapy was applied. Furthermore, Zhang et al. reported a link between PaO_2 and the severity of sepsis [19].

Nevertheless, PaO_2 is a quite simple and easy parameter to obtain in the hospital. The interest is limited for the management of pre-hospital patients, because arterial blood sample is sometime difficult to obtain in this setting. As for cardiac arrest and acute coronary syndrome, pulse oximetry is an alternative to guide oxygen delivery which should be discussed in sepsis [37]. An unsolved question concerns whether supra normal oxygen levels are also associated with cell damage and how strict should arterial oxygen concentration be optimal. A recent study observed the beneficial effect of moderate hyperoxemia [19]. Anyhow, two on-going randomized studies (NCT02321072 and NCT02378545) should soon provide answers to these issues.

5. Conclusion

In a single hospital setting, it was found that increased PaO_2 at ICU admission was associated with increased mortality in patients with septic shock subjected to pre-hospital invasive ventilation. Despite the lack of power, this work opens up new perspectives to reinforce optimal pre-hospital management of patients with septic shock requiring early invasive ventilation for optimal respiratory support. Further studies are needed to define accurate PaO_2 target for optimal oxygen therapy in this context. Larger multi-centric studies comparing oxygen conservative strategy versus liberal strategy are needed to confirm these preliminary data.

Conflicts of interest and funding

The authors report to have no conflicts of interest or received funding.

Authors contribution

- Study concept and design: Jouffroy.
- Acquisition of data: Castres Saint Martin, Jouffroy.
- Analysis and interpretation of data: Jouffroy.
- Drafting of the manuscript: Jouffroy, Saade.
- Critical revision of the manuscript for important intellectual content: Philippe, Carli, Vivien.

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