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Original Contribution

Pre-hospital mechanical ventilation in septic shock patients

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ABSTRACT

Background: Mechanical ventilation can cause deleterious effects on the lung and thus alter patient's prognosis.
The aim of this study was to describe the characteristics of prehospital mechanical ventilation in patients with septic shock requiring mechanical ventilation in the prehospital setting.
Methods: Patients with septic shock subjected to pre-hospital intubation and mechanical ventilation by a mobile intensive care unit were consecutively included and retrospectively analysed. Septic shock was defined according to the international sepsis-3 consensus conference. Patient's characteristics, interventions, prehospital ventilatory parameters and outcome were retrieved from medical records. The association between the tidal volume indexed on ideal body weight (VTIBW) and mortality at day 28 was evaluated.
Results: Fifty-nine patients were included. Septic shock was mainly associated with pulmonary (64%) infection. Mean pre-hospital VTIBW was 7 ± 1 $ml.kg^{-1}$ in the overall population. Mortality reached 42%. The AUC of VTIBW was 0.83 [0.72–0.94].
Using logistic regression model including: age, prehospital mean blood pressure, volume infused in the prehospital setting, FiO_2 and length of stay in the intensive care unit, the association with mortality remained significant for VTIBW (OR adjusted [CI95] = 4.11 [1.89–10.98]), VTIBW >8 $ml \cdot kg^{-1}$ (OR adjusted [CI95] = 8.29 [2.35–34.98]) and VTIBW <8 $ml \cdot kg^{-1}$ (OR adjusted [CI95] = 0.12 [0.03–0.43]).
Conclusion: In this retrospective study, we observed an association between mortality at day 28 and prehospital VTIBW in pre-hospital mechanically ventilated patients with septic shock. A VTIBW <8 $ml \cdot kg^{-1}$ was associated with a decrease and a VTIBW >8 $ml \cdot kg^{-1}$ with an increase in mortality.

1. Introduction

In France, chest pain, dyspnea, shock and neurological disorders are the most common complaints to call the SAMU "Service d'Aide Médicale Urgente" (SAMU) equivalent to the prehospital emergency medical services (EMS) [1]. In the context of septic shock, the management of acute respiratory failure and/or coma, i.e. when the Glasgow Coma Score is lower than 8, often requires early sedation and invasive ventilation before any hospital admission, meaning in the prehospital setting by an EMS team [2]. Mechanical ventilation remains an invasive treatment and can cause lung injury. Pulmonary deleterious effects of mechanical ventilation occurred early, within the first days, when patients where subjected to mechanical ventilation in the ICU [3] and within the first hours when performed in the operating room, independent of any associated primary lung injury, i.e. pneumonia [4,5]. High tidal volumes (>10 $ml \cdot kg^{-1}$), especially in the context of acute respiratory distress syndrome (ARDS), were reported to alter patients' outcome [6]. In the absence of ARDS, high tidal volumes were also reported to increase pulmonary pro-inflammatory mediators and complications in the ICU [3,7-11]. However, a low tidal volume strategy, as a standard practice in all patients receiving mechanical ventilation, is still controversial [12]. No guidelines have focused on the management of pre-hospital mechanical ventilation in these situations yet. Beyond the inherent deleterious impact of mechanical ventilation, sepsis increases susceptibility to ventilator-induced lung injury predisposing to ARDS occurrence.

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In this optic, a lung protective strategy including a low tidal volume seems warranted in these patients with risk factors to develop ARDS, i.e. septic shock [12,13].

The aim of this study was to describe the prehospital characteristics of ventilator settings in patients with septic shock subjected to pre-hospital mechanical ventilation prior to ICU admission and evaluate whether an association exists between the prehospital tidal volume and mortality at day 28.

2. Methods

The French EMS, SAMU, is composed of switchboard operators and physicians. The SAMU is reached dialing a national number, the number 15. Over the phone, a SAMU physician determines the appropriate level of care to dispatch to the scene, based on the patient's medical history and clinical features communicated by the patient himself, by a relative or by any witness. For life-threatening emergencies, a mobile intensive care unit (MICU) named "Service Mobile d'Urgence et de Réanimation" (SMUR) is dispatched. The SMUR is composed of a driver, a nurse and an emergency physician and is equipped with medical devices and drugs allowing initial management of main organs failure (neurological, respiratory and cardiovascular) [1]. Upon hospital arrival, the patient is either admitted to the emergency department or directly to the intensive care unit (ICU).

2.1. Study population

Between January 2014 and December 2017, all consecutive patients intubated and mechanically ventilated prior to their admission in the ICU of Necker hospital in Paris for septic shock were eligible. Necker hospital is an academic hospital located in the centre of Paris and affiliated to Paris 6 Descartes University. There is no adults' emergency department in the hospital. The ICU includes 12 beds for post-operative care, in-hospitalised patients and patients cared by MICU.

All patients were aged above 18 years. Septic shock was defined according to the international sepsis-3 consensus conference [14]. Only patients subjected to mechanical ventilation, instituted in the prehospital setting for respiratory distress or neurological failure by a MICU, were included and retrospectively analysed.

In keeping with the French legislation, the ethical committee considered that consent of patients was not mandatory for participation in this retrospective anonymous database study (Number: 2015-08-03-SC).

2.2. Data collection

Data were extracted from prehospital and hospital medical reports. In order to minimize the bias associated with data abstraction, data collection was performed at the hospital admission by a single investigator using a standardized template, defined prior to data collection [15].

Prehospital data included patients' demographic characteristics (age, weight, size and gender), initial (parameters retrieved at the first medical contact) prehospital vital signs (systolic, diastolic and mean blood pressure, heart rate, pulse oximetry (SpO2) and respiratory rate), initial pre-hospital ventilator settings (respiratory rate, tidal volume, positive end-expiratory pressure (PEEP) and inspired fraction of oxygen (FiO2)), and the duration of prehospital care. In France, the plateau pressure and the driving pressure are, to date, not measured in the prehospital setting.

In-hospital data included the PaO2/FiO2 ratio, with the PaO2 measured from an arterial blood sample performed immediately at ICU admission, length of stay in the ICU, comorbidities simplified acute physiology score (SAPS 2) [16] and mortality at day 28.

2.3. Statistical analysis

Tidal volume was indexed on real body weight (VTRBW) and on ideal body weight (VTIBW) estimated using the Lorentz formula. Quantitative characteristics of ventilatory parameters including respiratory rate, tidal volume (VT), PEEP and FiO2 measured in the prehospital setting were analysed.

Considering that a VT ranging from 6 to 8 ml/kg based on IBW is recommended in anesthesia [17] and that low VT values are warranted for patients at risk of ARDS [12], we choose a VT threshold of 8 $ml \cdot kg^{-1}$ IBW to distinguish between low and high VT.

The primary outcome was mortality at day 28.

The in-ICU treatments were consistent after hospital admission. The study was performed in one hospital, in one intensive care unit by a small team of physicians [5] without practices (protocols of cares) change over the study period, so that the risk of bias resulting from the confounding factor related to various in-ICU practices was considered negligible.

Predictive performance of **pre-hospital** VTIBW for mortality at day 28 was evaluated using adjusted average receiver operating characteristic (ROC) curve obtained by averaging 10,000 bootstrapped samples (sampling with replacement) in order to limit the statistical impact of outliers [12].

Thereafter, univariate and multivariable analyses using logistic regression were conducted to evaluate the relationship between all covariates and mortality at day 28. All p values were two-tailed and $p < 0.05$ was considered significant.

Data are expressed as mean ± standard deviation (SD), or median with 95% confidence interval [CI95] for non-normal variables, or number and percentage.

All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Fifty-nine patients with septic shock cared for in the prehospital setting and subjected to pre-hospital mechanical ventilation by a MICU team were included.

Populations' demographic and clinical characteristics are summarized in Table 1. The mean age was 64 ± 16 years and 35 patients (59%) were male.

The origin of septic shock was mainly pulmonary (64%), urinary (17%) and abdominal (10%) (Table 2).

The duration of prehospital care did not differ between alive and deceased patients (110 ± 49 min vs 99 ± 33 min respectively, $p = 0.36$; Table 1).

The median length of stay in the ICU reached 9 [4–17] days (Table 1), with no difference between alive and deceased patients (16 ± 15 days vs 11 ± 10 days respectively, $p = 0.12$; Table 1). Mortality reached 42% at day 28. No patient died prior to hospital arrival.

Mean VT was 500 ± 69 ml in the overall population, 469 ± 59 ml and 541 ± 59 ml in alive and deceased patients respectively ($p < 10^{-3}$). Mean VTRBW was 7 ± 1 $ml \cdot kg^{-1}$ in the overall population, 7 ± 2 $ml \cdot kg^{-1}$ and 8 ± 1 $ml \cdot kg^{-1}$ in alive and deceased patients respectively ($p < 0.05$). Mean VTIBW weight was 7 ± 1 $ml \cdot kg^{-1}$ in the overall population, 7 ± 1 $ml \cdot kg^{-1}$ and 8 ± 1 $ml \cdot kg^{-1}$ in alive and deceased patients respectively ($p < 10^{-3}$). In the overall population, 33 patients (56%) had a VTIBW <8 $ml \cdot kg^{-1}$ and 26 (44%) had a VTIBW >8 $ml \cdot kg^{-1}$ ($p < 10^{-3}$).

Among alive patients, 26 (76%) had a VTIBW <8 $ml \cdot kg^{-1}$ and 8 (24%) had a VTIBW >8 $ml \cdot kg^{-1}$ ($p < 10^{-3}$) while among deceased patients, 7 (28%) had a VTIBW <8 $ml \cdot kg^{-1}$ and 18 (72%) a VTIBW >8 $ml \cdot kg^{-1}$.

In the univariate analysis, mortality at day 28 was significantly associated with SAPS2, VT, VTRBW, VTIBW, VTIBW <8 $ml \cdot kg^{-1}$ and VTIBW >8 $ml \cdot kg^{-1}$ (Table 3).

Using logistic regression model, including age, prehospital mean blood pressure, prehospital fluid expansion, FiO2 and the length of stay in the ICU, association with mortality at day 28

Table 1
Demographic, clinical and biological characteristics of patients with septic shock subjected to prehospital mechanical ventilation.
Quantitative variables are expressed as mean ± standard deviation. Qualitative variables are expressed as absolute value and percentage. Non-parametric variables are expressed as median ± minimal and maximal values.

	Alive at day 28 (n = 34)	Deceased at day 28 (n = 25)	Overall population (n = 59)
Age (years)	63 ± 16	66 ± 16	64 ± 16
Male gender	9 (26%)	16 (64%)	35 (59%)
Mean blood pressure (mm Hg)	75 ± 27	68 ± 22	72 ± 26
Systolic blood pressure (mm Hg)	103 ± 34	82 ± 28	98 ± 32
Diastolic blood pressure (mm Hg)	62 ± 26	58 ± 20	31 ± 24
Heart rate (beats/min)	121 ± 25	108 ± 33	116 ± 29
Pulse oximetry (%)	86 [56–100]	88 [40–97]	88 [40–100]
Respiratory rate (moves/min)	14 [10–30]	15 [12–30]	15 [10–30]
Duration of prehospital care (min)	110 ± 49	99 ± 33	105 ± 43
Length of stay into ICU (days)	9 [4–17]	5 [3–14]	12 [5–20]
Prehospital fluid volume expansion (ml)	1000 [250–3000]	750 [250–3000]	1000 [250–3000]
SAPS2	69 (18–113)	89 (26–135)	74 (18–135)
PEEP	5 ± 2	5 ± 1	5 ± 1
PaO2/FiO2	174 ± 77	220 ± 80	194 ± 81
Tidal volume (ml)	457 ± 68	541 ± 59	493 ± 76
Tidal volume indexed on body weight	7 ± 2	8 ± 1	7 ± 1
Tidal volume indexed on IBW	7 ± 1	8 ± 1	7 ± 1
Tidal volume indexed on IBW > 8 $ml \cdot kg^{-1}$	10 (29%)	15 (60%)	19 (32%)
Tidal volume indexed on IBW < 6 $ml \cdot kg^{-1}$	23 (68%)	2 (8%)	14 (24%)
Tidal volume indexed on IBW 6–8 $ml \cdot kg^{-1}$	1	8	9

Legend: PEEP: positive end-expiratory pressure, ICU: intensive care unit, IBW: ideal body weight, SAPS: simplified acute physiology score, PaO2/FiO2: ratio between arterial partial pressure of dioxygen and inspired fraction of dioxygen.

Table 2
Origin of sepsis of patients with septic shock subjected to prehospital mechanical ventilationData are expressed as absolute value with percentage.

Site of infection	n	Percentage
Pulmonary	38	64%
Urinary	10	17%
Digestive	6	10%
Cutaneous	2	3.5%
Invasive medical device	2	3.5%
Meningeal	1	2%

remained significant for VTIBW (OR adjusted [CI95] = 4.11 [1.89–10.98]), VTIBW >8 $ml \cdot kg^{-1}$ (OR adjusted [CI95] = 8.29 [2.35–34.98]) and VTIBW <8 $ml \cdot kg^{-1}$ (OR [CI95] = 0.12 [0.03–0.43]).

The area under the average ROC curves [CI 95] (Fig. 1) of prehospital VTRBW and VTIBW were of 0.70 [0.56–0.83] and 0.83 [0.72–0.94] respectively for mortality at day 28.

4. Discussion

In this retrospective study, we report an association between mortality at day 28 and prehospital VTIBW in septic shock patients mechanically ventilated in the prehospital setting. A VTIBW <8 $ml \cdot kg^{-1}$ was associated with decreased mortality while a VTIBW >8 $ml \cdot kg^{-1}$ with an increase in mortality.

The deleterious effects of mechanical ventilation are well established contributing to aggravate existing pulmonary lesions. Lung injury is worsened in patients without any previous pulmonary damage but at risk of ARDS in the case of sepsis, trauma, multiple transfusions and high-risk surgery [18,19]. Over the past 30 years [6,20], the lung-protective ventilation strategy has become a standard of care for ARDS [21]. To date, a low tidal volume of 4–8 $ml \cdot kg^{-1}$ indexed on predicted body weight, a maximum plateau pressure of 30 cm H_2O and manageable use of PEEP, remain core elements of this strategy [22,23]. The systematic use of a low VT in all mechanically ventilated patients is not yet recommended despite the undeniable protective effect of reduced VT [12]. As pulmonary deleterious effects of mechanical ventilation occurred early [3-5], lung protective strategy with VT reduction, it appears logical to apply it as early as in the prehospital setting especially for patients with risk of ARDS occurrence.

Table 3
Univariate analysis of factors associated with mortality at Day 28 in patients with septic shock subjected to prehospital mechanical ventilation.
Data are presented as p values and Odds Ratio (OR) with a 95% confidence interval [95% CI].

Variables	Univariate analysis	
	OR [95% CI]	p value
Age (years)	1.01 [0.98–1.05]	0.47
Male	0.71 [0.24–2.04]	0.53
Mean blood pressure (mm Hg)	0.99 [0.97–1.01]	0.30
Systolic blood pressure (mm Hg)	0.99 [0.97–1.01]	0.99
Diastolic blood pressure (mm Hg)	1.01 [0.99–1.02]	0.50
Heart rate (beats/min)	0.98 [0.96–1.01]	0.11
Pulse oximetry (%)	0.99 [0.95–1.03]	0.70
Respiratory rate (moves/min)	1.04 [0.91–1.21]	0.56
Duration of prehospital care (min)	0.99 [0.98–1.01]	0.36
Length of stay into ICU (days)	0.96 [0.91–1.01]	0.12
Prehospital fluid volume expansion (ml)	1.00 [0.99–1.01]	0.25
SAPS2	1.03 [1.01–1.05]	0.04
PEEP	1.00 [0.70–1.45]	0.98
PaO2/FiO2	1.01 [0.99–1.02]	0.03
Tidal volume (ml)	1.02 [1.01–1.04]	0.001
Tidal volume expansion indexed on body weight	1.06 [0.47–2.33]	0.01
Tidal volume expansion indexed on IBWt	3.69 [1.96–8.43]	0.0004
Tidal volume expansion indexed on IBW > 8 $ml \cdot kg^{-1}$	11.25 [3.26–47.27]	0.0003
Tidal volume expansion indexed on IBW < 6 $ml \cdot kg^{-1}$	0.16 [0.03–0.67]	0.03

Legend: PEEP: positive end-expiratory pressure, ICU: intensive care unit, IBW: ideal body weight, SAPS: simplified acute physiology score, PaO2/FiO2: ratio between arterial partial pressure of dioxygen and inspired fraction of dioxygen.

The out-of-hospital time is this study may appear long but reflects the French practices. The Franco-European model of prehospital care is based on the SAMU-SMUR. Contrary to the North American emergency medical service based on paramedics, the SMUR is composed by a nurse and a physician who provide cares since the pre-hospital setting. As intubation and mechanical ventilation require time, that explains the apparent long delays before hospital admission.

This study includes limitations. First, this is a retrospective and single centre study with a small sample size. Second, ventilator parameters set in the ICU were no taken into account, because the prognosis impact of ventilatory support in the ICU was not the purpose of this study. Third, a sorting bias may exist as data were retrospectively collected from medical reports. Fourth, this work selected patients with septic shock and is consequently not extrapolable to other situations.

Despite these limitations, this study reinforces the need for standards of care to improve pre-hospital mechanical ventilation, particularly in septic shock patients at high risk of ARDS [24,25]. Larger cohorts are needed to confirm these preliminary results.

5. Conclusion

We report an association between mortality at day 28 and prehospital tidal volume in septic shock patients mechanically ventilated in the prehospital setting. A tidal volume indexed on ideal

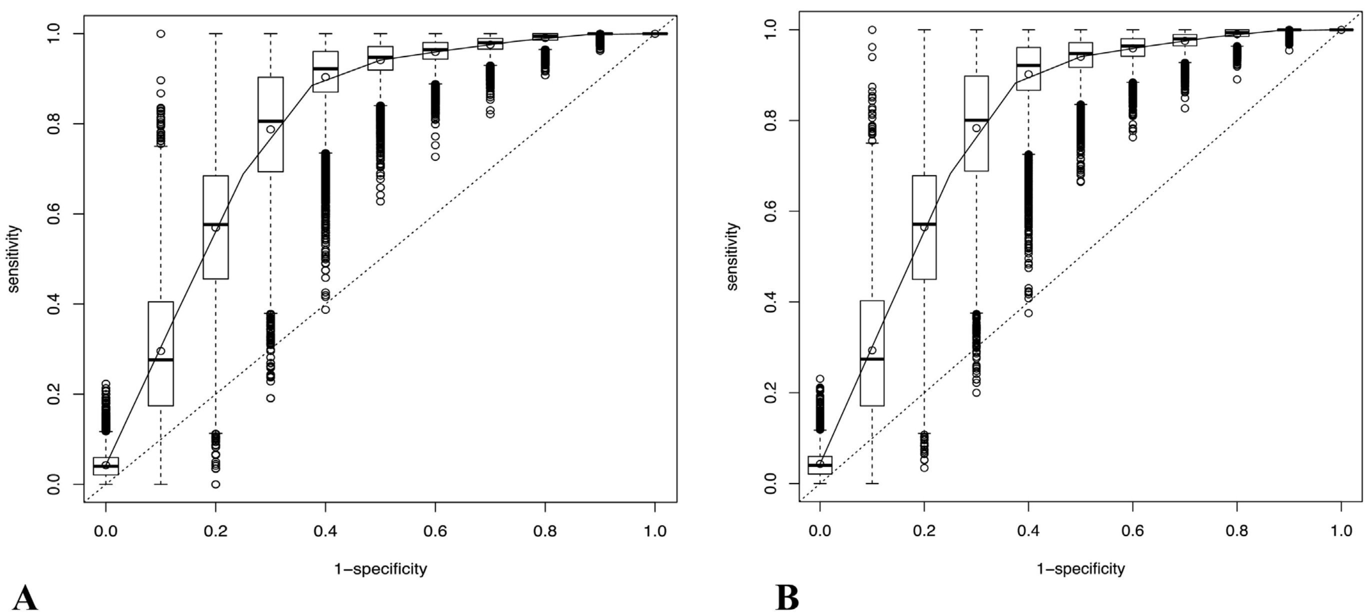

Fig. 1. Out-of-hospital tidal volume average ROC curves for prediction of mortality at day 28.(A) out-of-hospital tidal volume indexed on BW and on IBW (B) out-of-hospital tidal volume indexed on IBW, average ROC curves for prediction of mortality at day 28.The dotted line represents the non-discrimination curve.

body weight <8 ml·kg^{-1} was associated with decreased mortality while a tidal volume indexed on ideal body weight >8 ml·kg^{-1} with an increase in mortality.

These results underline the need to optimize the management of pre-hospital mechanical ventilation particularly in patients at risk of ARDS.

Authors contribution

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

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The authors declare no competing interests

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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