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Assessment of tissue oxygenation to personalize mean arterial pressure target in patients with septic shock

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ABSTRACT

Keywords:

Intensive care unit
Near-infrared spectroscopy
Recovery slope
Tissue oxygenation

Objective: To investigate whether assessment of tissue oxygenation could help personalizing the mean arterial pressure (MAP) target in patients with septic shock.

Methods: We prospectively measured near-infrared spectroscopy variables in 22 patients with septic shock receiving norepinephrine with a MAP > 75 mmHg within the first six hours of intensive care unit (ICU) stay for patients with community-acquired septic shock and within the first six hours of resuscitation for patients with ICU-acquired septic shock. All measurements were performed at MAP > 75 mmHg (“high-MAP”) and at MAP 65–70 mmHg (“low-MAP”) after decreasing the norepinephrine dose. Relative changes in StO₂ recovery slope (RS) > 8% were considered clinically relevant.

Results: After decreasing the norepinephrine dose by $45 \pm 24\%$, MAP significantly decreased from 81 [78;84] to 68 [67;69] mmHg, whereas cardiac index did not change. On average, the StO₂-RS significantly decreased between high and low-MAP from 2.86 [1.87;4.32] to 2.41 [1.14;3.72] %/sec with a large interindividual variability: the StO₂-RS decreased by > 8% in 14 patients, increased by > 8% in 4 patients and changes were < 8% in 4 patients. These changes in StO₂-RS were correlated with the StO₂-RS at low-MAP ($r = 0.57, p = 0.006$). At high-MAP, there was no difference between patients exhibiting a relevant decrease or increase in StO₂-RS.

Conclusions: A unique MAP target may not be suitable for all patients with septic shock as its impact on peripheral oxygenation may widely differ among patients. It could make sense to personalize MAP target through a multimodal assessment including peripheral oxygenation.

1. Introduction

Septic shock is one of the main causes of admission in critically ill patients and its mortality remains high (Rhodes et al., 2016). In addition to macrocirculatory abnormalities, septic shock is also characterized by microcirculatory abnormalities (De Backer et al., 2002; Ince, 2005; Vincent and De Backer, 2005; Trzeciak et al., 2008), which contribute to tissue hypoxia and are also closely linked to outcome (De Backer et al., 2013).

The mean arterial pressure (MAP) is the upstream pressure for the perfusion of most vital organs. The Surviving Sepsis Campaign guidelines recommend to initially target a MAP ≥ 65 mmHg in patients with

septic shock (Rhodes et al., 2016). Vasopressors are often used for this purpose, especially when the vasomotor tone is depressed. However, excessive vasoconstriction might be deleterious on the microcirculation (Dubin et al., 2009). Recently, Fiorese Coimbra et al. demonstrated that increasing MAP from 65 to 70 to 85–90 mmHg resulted in a significant improvement in sublingual microcirculation in patients with septic shock, regardless a medical history of arterial hypertension (Fiorese Coimbra et al., 2019). This suggests that targeting a MAP > 85 mmHg with vasopressors in patients with septic shock is on average beneficial in terms of microcirculation, although the individual behavior of microcirculation and tissue oxygenation induced by MAP changes remains unclear (Dubin et al., 2009; Thooft et al., 2011). Thus, whether

Abbreviations: MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; SAPS, simplified acute physiology score; StO₂, muscle tissue oxygenation; VOT, vascular occlusion test

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assessment of tissue oxygenation and microcirculation could help intensivists to personalize the MAP target in such patients is still unresolved.

Peripheral oxygenation can be assessed at the bedside by using near-infrared spectroscopy (NIRS) through the measurement of the muscle tissue oxygenation (StO₂) and the StO₂ recovery slope, which reflects the capacity of microvessels to dilate and/or to be recruited in response to a local hypoxic stimulus induced by a vascular occlusion test (VOT) (Mayeur et al., 2011). In patients with septic shock, the StO₂ recovery slope, unlike the StO₂, was shown to be an independent prognostic factor (Creteur et al., 2007; Shapiro et al., 2011) and thus could be an interesting parameter to personalize the MAP target in patients with septic shock.

Thus, we conducted a prospective study in our unit to assess in patients with septic shock and MAP > 75 mmHg (called “high-MAP”) whether lowering MAP to 65–70 mmHg (called “low-MAP”) had an impact on the StO₂ recovery slope.

2. Material and methods

The study was approved by the Institutional Review Board of our institution (Comité pour la Protection des Personnes Paris VII, number IDRCB A00132-55). Informed consent was given by all patients or their next of kin.

2.1. Study population

We included consecutive patients within the first six hours of intensive care unit (ICU) stay for patients with community-acquired septic shock and within the first six hours of resuscitation for patients with ICU-acquired septic shock for whom: 1) the MAP was > 75 mmHg after initial resuscitation (fluid and norepinephrine), and 2) the physician in charge decided to decrease the norepinephrine dose to target 65–70 mmHg of MAP. All patients should have been already monitored with a PiCCO-2 device (Pulsion Medical Systems, Feldkirchen, Germany), mechanically ventilated in volume assist control mode and sedated. Exclusion criteria were patients < 18 years old, patients with arterio-venous fistula contraindicating VOT, the need for therapeutic changes during the study period or in cases of withdrawal of informed consent.

2.2. NIRS variables

The StO₂ was measured with the InSpectra Tissue oxygenation monitor, model 650 (Hutchinson Technology, Hutchinson, MN), after placing a NIRS probe with a 15-mm distance between illumination and detection optical fibers on the thenar eminence. After at least one minute of signal stabilization, StO₂ values were measured continuously and stored every two seconds before and after VOT. The VOT was performed with a pneumatic cuff placed around the forearm and rapidly inflated to 220 mmHg and kept inflated until StO₂ dropped to 40% (Mayeur et al., 2011). The StO₂ recovery slope and the other NIRS variables were automatically calculated offline by the InSpectra Analysis Program V4.00 (Hutchinson Technology, Hutchinson, MN), as previously described (Mayeur et al., 2011).

2.3. Transpulmonary thermodilution measurements

All patients had a central venous catheter inserted in the superior vena cava territory into the internal jugular vein and a thermistor-tipped arterial catheter placed into the femoral artery. All thermodilution measurements were performed by injecting a 15-mL bolus of cold saline through the central venous catheter. The average result from three consecutive 15-mL injections was recorded for each patient (Monnet et al., 2011).

2.4. Study design

A first set of measurements was performed at high-MAP. The norepinephrine dose was then decreased to target low-MAP. After a 30-min stabilization period, a second set of measurements was performed.

2.5. Statistical analysis

Variables were summarized as median [interquartile] or counts and percentages. Comparisons were performed using a Fisher's exact test for categorical variables and using a Mann-Whitney *U* test or a Wilcoxon test for continuous variables. Correlations were assessed by Spearman's coefficient of rank correlation. We considered as relevant a relative change in StO₂ recovery slope > 8% (Mayeur et al., 2011). Statistical analysis was performed with MedCalc 11.6.0 software (MedCalc, Mariakerke, East Flanders, Belgium) and a *p* value < 0.05 was considered statistically significant.

3. Results

3.1. Study population

The study was prematurely stopped after the inclusion of 22 patients, as NIRS probes were no longer commercialized in Europe. Among the 22 patients (67[57;77] years old, SAPSII 56[45;68], 50% of men), 17 (77%) had history of chronic hypertension and/or diabetes mellitus. The ICU mortality was 27%. Pneumonia was the source of infection in 77% of patients and 14% of patients had ICU-acquired septic shock. The other baseline characteristics of patients are summarized in Table 1. To achieve low-MAP, the norepinephrine dose (0.68[0.45;1.22]µg/kg/min) was decreased by 45 ± 24%. MAP significantly decreased from 81[78;84] to 68[67;69]mmHg whereas the cardiac index remained unchanged (Table 2).

3.2. Effects of MAP changes on StO₂ recovery slope

In the whole population, the StO₂ recovery slope significantly decreased between high and low-MAP from 2.86 [1.87;4.32] to 2.41 [1.14;3.72]%/*sec* (*p* = 0.02) (Table 2, Fig. 1A). The StO₂ recovery slope decreased by > 8% in 14 patients, increased by > 8% in 4 patients and changes were < 8% in 4 patients (Fig. 1B). The percent changes in StO₂ recovery slope were correlated with the StO₂ recovery slope at low-MAP (*r* = 0.57, *p* = 0.006) (Fig. 2) but not with changes in MAP (*r* = 0.36, *p* = 0.10) or in cardiac index (*r* = 0.38, *p* = 0.08). The StO₂ recovery slope at low-MAP was lower in patients exhibiting a > 8% decrease than in patients exhibiting a > 8% increase in StO₂

Table 1
Patients' characteristics at baseline.

Variables	Value	
Age (years)	67	[57;77]
Male (n,%)	11	(50%)
SAPS II	56	[45;68]
SOFA score	12	[8;13]
Body mass index (kg/m ²)	26	[21;29]
Hypertension (n,%)	17	(77%)
Diabetes mellitus (n,%)	9	(41%)
Obliterant arteriopathy (n,%)	4	(18%)
Use of corticosteroids (n,%)	5	(23%)
Fraction of inspired oxygen (%)	50	[40;70]
C-Reactiv-Protein (mg/L)	211	[102;297]
Hemoglobin (g/dL)	10.5	[9.2;11.5]

n = 22.

Data are expressed as median [interquartile] or counts (percentages).

SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment.

Table 2
Macrocirculatory, NIRS and metabolic variables of patients at high and low mean arterial pressure target.

Variables	Value			
	High-MAP		Low-MAP	
Macrocirculatory variables				
Dose of norepinephrine (µg/kg/min)	0.68	[0.45;1.22]	0.36	[0.27;0.60]*
MAP (mmHg)	81	[78;84]	68	[67;69]*
Heart rate (beats/min)	89	[78;104]	87	[79;102]
Cardiac index (L/min/m ²)	3.22	[2.40;4.10]	3.12	[2.28;3.93]
SVRI (dynes.sec/cm ⁵ /m ²)	1916	[1579;2604]	1786	[1444;2256]*
NIRS variables				
StO ₂ (%)	80	[77;89]	79	[75;90]
Peak of StO ₂ (%)	91	[90;96]	90	[86;95]
Occlusion slope (%/min)	-8.76	[-10.86;-7.26]	-9.00	[-10.79;-7.96]
Recovery slope (%/sec)	2.86	[1.87;4.32]	2.41	[1.14;3.72]*
Hyperemia recovery area (arbitrary units)	13.12	[9.65;25.09]	11.65	[7.49;19.13]
Metabolic variables				
Temperature (°C)	36.8	[35.7;37.4]	36.9	[36.0;37.5]
SpO ₂ (%)	99	[96;100]	99	[96;100]
PaO ₂ /FiO ₂ ratio	211	[155;280]	242	[160;289]
Lactate (mmol/L)	1.7	[1.1;2.8]	1.7	[1.2;2.5]
Hemoglobin (g/dL)	10.6	[9.3;11.9]	10.3	[9.1;11.1]

n = 22. Data are expressed as median [interquartile].

MAP: mean arterial pressure; SVRI: indexed systemic vascular resistance; NIRS: near-infrared spectroscopy;

StO₂: muscle tissue oxygen saturation; SpO₂: pulsed oxygen saturation; PaO₂: partial pressure of arterial oxygen; FiO₂: fraction of inspired oxygen.

* p < 0.05, low vs. high-MAP.

recovery slope (1.97[1.10;2.58] vs. 3.73[3.68;4.50]/%/sec, respectively, p = 0.004).

At high-MAP, there was no difference in demographic, macrocirculatory, NIRS and metabolic variables between patients exhibiting a > 8% decrease or a > 8% increase in StO₂ recovery slope between high and low-MAP (Table 3). Changes in StO₂ recovery slope were not different between patients with and without history of chronic hypertension or diabetes mellitus.

3.3. Effects of MAP changes on the other NIRS parameters

In the whole population, the StO₂ was unchanged between high and low-MAP (80[77;89] vs. 79[75;90]%, p = 0.48) (Table 2). The StO₂ was not different between high and low-MAP in patients with > 8% decrease (79[77;83] vs. 78[75;83]%, respectively, p = 0.45) or > 8% increase (87[78;91] vs. 85[78;92]%, respectively, p = 0.88) in StO₂ recovery slope.

In the whole population, the StO₂ occlusion slope (-8.76[-10.86;-7.26] vs. -9.00[-10.79;-7.96]/%/min, p = 0.73) and the hyperemia recovery area were unchanged between high and low-MAP (Table 2). The StO₂ occlusion slope decreased in 12 patients and increased in 10 patients.

4. Discussion

The individual behavior of microcirculation and tissue oxygenation induced by MAP changes in patients with septic shock is still matter of debate. Here, we aimed at presenting the individual changes of StO₂ recovery slope following MAP decrease in patients after the resuscitation phase of septic shock. We found that decreasing MAP from high to low target by decreasing the norepinephrine dose induced a decrease in StO₂ recovery slope without changes in hyperemia recovery area between high and low MAP. As the latter finding suggests endothelial function did not changes in changes with MAP, the observed changes in StO₂ recovery slope likely depended on changes in tissue perfusion pressure (Mesquida et al., 2012) with a better thenar muscle perfusion pressure at high MAP than at low MAP. However, we evidenced a large interindividual variability in changes in StO₂ recovery slope following MAP decrease. Moreover, these changes in StO₂ recovery slope were not correlated with changes in macrocirculatory variables, illustrating a possible loss of hemodynamic coherence (Ince, 2015). Finally, although the StO₂ occlusion slope remained unchanged between high-MAP and low MAP, we evidenced as for the StO₂ recovery slope, a large interindividual variability in changes in StO₂ occlusion slope following MAP decrease. This suggests that the ability of the thenar eminence muscles to use the oxygen delivered for a given MAP target may differ from patient to patient.

Previous studies suggested that targeting a MAP at 85–90 mmHg in patients with septic shock is on average beneficial in terms of

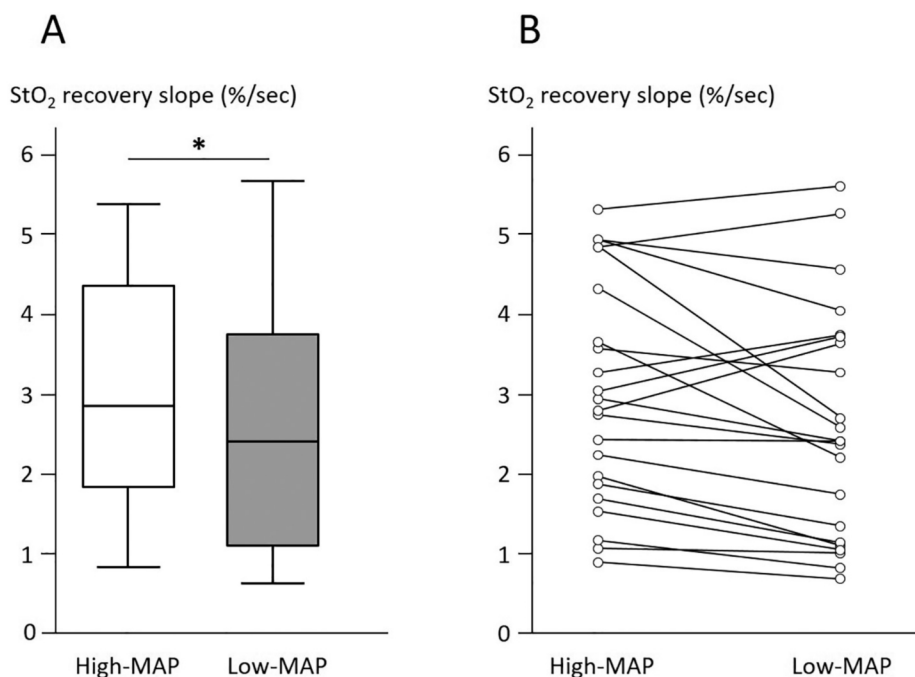


Fig. 1. Panel A: Muscle tissue oxygen saturation (StO₂) recovery slope at high and low mean arterial pressure (MAP) target. Open box: high-MAP and black box: low-MAP. The box show the 25th and 75th percentiles, the line in the box the median and the whiskers the minimum and maximum values, n = 22. *p < 0.05 low vs. high-MAP.

Panel B: Individual changes in muscle tissue oxygen saturation (StO₂) recovery slope between high and low mean arterial pressure (MAP) target, n = 22.

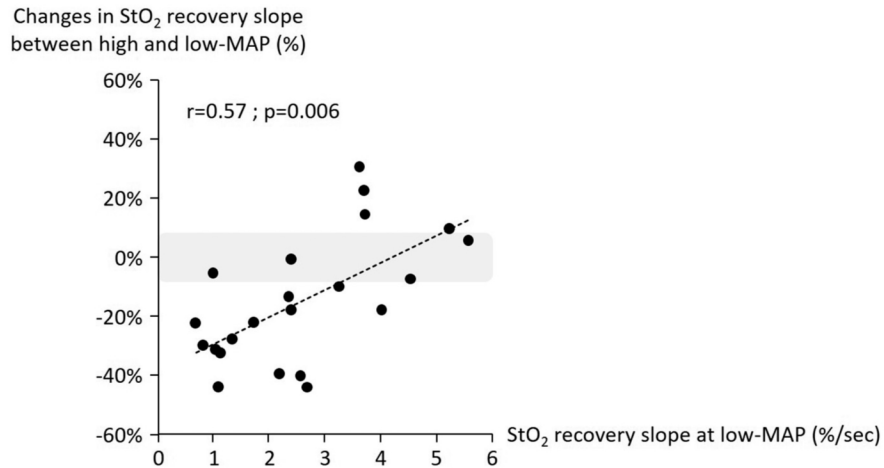


Fig. 2. Relative changes (in %) in muscle tissue oxygen saturation (StO₂) recovery slope between high and low mean arterial pressure (MAP) target (y-axis) according to the StO₂ recovery slope at low-MAP (x-axis). The grey zone represents the non-relevant (< 8%) changes in StO₂ recovery slope.

microcirculation (Fiorese Coimbra et al., 2019; Thooft et al., 2011). However, the effects of MAP changes on microcirculation and tissue oxygenation could differ from one patient to another. Here, we evidenced a large interindividual variability in changes in StO₂ recovery slope following MAP decrease in patients with septic shock with two opposite behaviors: the StO₂ recovery slope seems to be greater at the high MAP level in the majority of patients but greater at the low MAP level in a smaller group of patients. Such an interindividual variability

in the StO₂ recovery slope changes could firstly depend on the state of the microcirculation. Dubin et al. showed that increasing MAP in patients with septic shock improved sublingual microcirculation only in patients with impaired microcirculation at baseline (Dubin et al., 2009). Similarly, we found that changes in StO₂ recovery slope between high and low-MAP were correlated with the StO₂ recovery slope at low-MAP. Furthermore, 93% of patients exhibiting a > 8% decrease in StO₂ recovery slope between high and low-MAP had abnormally low

Table 3

Demographic, macrocirculatory, NIRS and metabolic variables at high mean arterial pressure target in patients with relevant changes in StO₂ recovery slope between high and low mean arterial pressure target.

Variables	Value	
	Decrease in StO ₂ recovery slope from high to low-MAP > 8% (n = 14)	Increase in StO ₂ recovery slope from high to low-MAP > 8% (n = 4)
Demographic variables		
Age (years)	70 [56;79]	69 [58;80]
Male (n,%)	8 (57%)	2 (50%)
SAPS II	55 [45;68]	57 [46;64]
SOFA score	13 [8;14]	10 [8;12]
Body mass index (kg/m ²)	26 [21;29]	28 [23;33]
Hypertension (n,%)	12 (86%)	3 (75%)
Diabetes mellitus (n,%)	8 (57%)	1 (25%)
Obliterant arteriopathy (n,%)	3 (21%)	1 (25%)
Use of corticosteroids (n,%)	3 (21%)	1 (25%)
Macrocirculatory variables at high MAP		
Doses of norepinephrine (µg/kg/min)	0.73 [0.48;1.44]	0.84 [0.26;1.40]
MAP (mmHg)	81 [80;83]	78 [77;82]
Heart rate (beats/min)	88 [71;101]	98 [81;113]
Cardiac index (L/min/m ²)	3.64 [2.40;4.59]	2.70 [2.19;3.38]
SVRI (dyne.sec/cm ⁵ /m ²)	1793 [1392;2595]	2024 [1699;2544]
NIRS variables at high MAP		
StO ₂ (%)	80 [77;83]	88 [78;91]
Peak of StO ₂ (%)	91 [89;94]	93 [86;97]
Occlusion slope (%/min)	-8.77 [-10.86;-7.60]	-8.17 [-9.99;-5.54]
Recovery slope (%/sec)	2.49 [1.69;3.65]	3.15 [2.91;4.05]
Hyperemia recovery area (arbitrary units) x min	15.33 [10.60;25.27]	10.29 [7.66;13.89]
Metabolic variables at high MAP		
Temperature (°C)	37.1 [35.9;37.6]	35.7 [35.4;36.5]
SpO ₂ (%)	98 [96;100]	99 [98;100]
PaO ₂ /FiO ₂ ratio	174 [111;242]	198 [160;304]
Lactate (mmol/L)	1.7 [1.2;3.0]	2.5 [0.9;4.0]
Hemoglobin (g/dL)	10.2 [9.2;11.6]	11.0 [9.3;11.5]

n = 18. Data are expressed as median [interquartile] or counts (percentages).

MAP: mean arterial pressure; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment; SVRI: indexed systemic vascular resistance; NIRS: near-infrared spectroscopy; StO₂: muscle tissue oxygen saturation; SpO₂: pulsed oxygen saturation; PaO₂: partial pressure of arterial oxygen; FiO₂: fraction of inspired oxygen.

StO₂ recovery slope at low-MAP. Secondly, this interindividual variability could be explained by the potential opposite effects of the norepinephrine dose on microvascular blood flow (Legrand et al., 2019). Decreasing the norepinephrine dose might decrease the microvascular blood flow in pressure-dependent vascular beds but might also decrease the excessive local vasoconstriction and thus improve the microvascular blood flow.

Changes in StO₂ recovery slope following MAP decrease appeared unpredictable. There was no difference in demographic, macrocirculatory and metabolic variables measured at high-MAP in patients exhibiting a > 8% decrease or a > 8% increase in StO₂ recovery slope. Interestingly, patients had similar high StO₂ values at high and low-MAP, regardless the StO₂ recovery slope changes. The StO₂ is a measure of the saturation of oxygen hemoglobin in microvessels (Ward et al., 2006) and is mainly driven by the O₂ saturation of the venular blood (Moens et al., 2005). Such high StO₂ values, previously reported in patients with septic shock (Pareznik et al., 2006; Skarda et al., 2007; Leone et al., 2009), even in severely hypotensive patients (Georger et al., 2010), can be explained by the presence of arterio-venous shunting, which result in increased O₂ saturation of the venous blood. In this regard, others previously demonstrated that the StO₂, unlike the StO₂ recovery slope, was not an independent prognostic factor in patients with septic shock (Creteur et al., 2007; Shapiro et al., 2011), although some authors reported that persisting low StO₂ (< 70%) after a 8-h period of shock resuscitation was associated with poor outcome (Lima et al., 2009).

Finally, we found no correlation between changes in StO₂ recovery slope and changes in MAP or cardiac index, highlighting the potential loss of hemodynamic coherence in patients with septic shock (Ince, 2015), as demonstrated in previous studies (De Backer et al., 2013; Fiorese Coimbra et al., 2019; Trzeciak et al., 2007).

Overall, our results suggest that a unique MAP target for every patient with septic shock is probably not suitable. It might be more valuable to personalize MAP target through a multimodal assessment that includes not only central but also peripheral markers of perfusion and/or tissue oxygenation.

We acknowledge some limitations to our study. First, we investigated one peripheral territory and we cannot exclude that the norepinephrine effects on MAP could be different in other territories, as previously illustrated (Jhanji et al., 2009). Second, the large interindividual variability in changes in StO₂ recovery slope may also depend on patient-related factors other than MAP. Nevertheless, it must be noted that there was no difference in demographic, macrocirculatory and metabolic variables between patients exhibiting a decrease or increase in StO₂ recovery slope. Third, due to the design of our clinical study, we studied StO₂ recovery slope changes following a MAP decrease. Our results cannot prejudge the potential StO₂ recovery slope changes following a MAP increase during the resuscitation phase of septic shock. Four, central venous oxygen saturation was not recorded and endothelial function was not directly investigated.

5. Conclusions

The conclusions of our study are twofold. First, this study only alerts us to the fact that the same MAP target is probably not suitable for all patients with septic shock. Second, it might be interesting to personalize the MAP target in patients with septic shock through a multimodal assessment that includes not only central but also peripheral markers of perfusion and/or oxygenation whatever the technique used and not necessarily with the NIRS technology.

CRedit authorship contribution statement

Mathieu Jozwiak, Xavier Monnet, Jean-Louis Teboul: Conceptualization

Matthieu Chambaz, Pierre Sentenac: Investigation

Mathieu Jozwiak, Matthieu Chambaz, Pierre Sentenac, Jean-Louis Teboul: Formal analysis

Mathieu Jozwiak, Xavier Monnet, Jean-Louis Teboul: Supervision

Mathieu Jozwiak, Xavier Monnet, Jean-Louis Teboul: Validation
Mathieu Jozwiak, Matthieu Chambaz, Pierre Sentenac, Xavier Monnet, Jean-Louis Teboul Writing - Original draft

Mathieu Jozwiak, Jean-Louis Teboul: Writing - review & editing

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JLT and XM are members of the medical advisory board of Pulsion Medical Systems. The other authors have no conflict of interest to declare.

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