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Associations between peripheral perfusion disorders, mean arterial pressure and the dose of norepinephrine administered in early phase of septic shock.

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Abstract:

The aim of the study was to explore the correlations between peripheral perfusion, mean arterial pressure and the dose-rate of norepinephrine (NE) infused for the treatment. The study is retrospective analysis of data acquired prospectively on 57 patients during the first 24 hours of a septic shock. We collected clinical and circulatory characteristics, skin perfusion assessment (Capillary refill time (CRT), mottling score and temperature gradients) and the dose rate of NE infusion. There were negative correlations between mean arterial pressure (MAP) and temperature gradients (core-to-toe $P = 0.03$, core-to-index $P = 0.04$) and abnormal CRT was associated with lower MAP ($P = 0.02$). The dose of NE was correlated with temperature gradient (core-to-toe: $P = 0.02$, core-to-index: $P = 0.01$, forearm-to-index: $P = 0.008$) in the overall population. In patients receiving NE for at least 12h, NE dose was correlated mottling score ($P = 0.006$), temperature gradients (core-to-toe, $P = 0.04$, forearm-to-index: $P = 0.02$, core-to-index: $P = 0.005$) and CRT ($P = 0.001$). The dose of NE administered was associated with 14-days mortality (OR = 1.21 [1.06 – 1.38], $P = 0.006$) and with 28-days mortality (OR = 1.17 [1.01 – 1.36], $P = 0.04$). In conclusion, the study described the presence of correlations between peripheral perfusion and MAP and between peripheral perfusion and the dose rate of NE infusion.

Keywords:

- Norepinephrine
- Peripheral perfusion
- Septic shock
- Thermography

Introduction

Septic shock is a complex critical condition associated with a high mortality rate generally around 30 to 40%.^{1,2} It is the most severe form of sepsis, which involves hemodynamic failures and immune, inflammatory and metabolic disorders. These pathophysiologic alterations finally leads to a circulatory shock including tissue perfusion disorders causing organ failures and associated with deaths^{3,4}.

The study of peripheral perfusion and regional tissue perfusion in patients with septic shock is an emerging issue in recent years. Indeed, many studies underline the interest of the monitoring of parameters that evaluate the regional perfusion in these patients to better evaluate the prognosis of the patients. Mottling score⁵, capillary refill time (CRT)⁶ and temperature gradients⁷ are associated with mortality. In addition, it appears that tissue perfusion disorders is associated with the presence of organ failure⁷⁻⁹. Thus, maintaining organ perfusion in the time-course of septic shock is a fundamental goal. Therefore, it is important to better understand how to detect the presence of peripheral hypoperfusion.

Some authors suggest that correcting peripheral perfusion disorders could reduce the number of organ failures and thus mortality^{4,10}. Therefore, they suggest that peripheral perfusion parameters should be used as objectives to guide therapeutic management¹¹⁻¹³. The studies performed seem to support the idea of improved management of patients in septic shock when peripheral perfusion parameters are used as treatment goals. Van Genderen reported a reduction in the amount of fluid administered¹⁴. In the ANDROMEDA-SHOCK study, Hernandez et al reported a reduction in the number of organ failures without reduction in mortality when therapeutic management was guided based on CRT normalization¹². Mean arterial pressure (MAP) is one of the parameters conventionally used to guide the resuscitation of patients today¹⁵. It therefore seems interesting to study the associations between peripheral perfusion parameters and MAP.

The management of patients with septic shock is largely based on the use of vasopressors, which can have a beneficial effect on tissue perfusion by improving systemic hemodynamics but can also be the cause of tissue perfusion disorders, secondary to deleterious vasoconstriction^{16,17}, and can influence peripheral perfusion parameters. So, we need to better understand the relationship between norepinephrine administration and peripheral perfusion alterations.

Consequently, the aim of the study was to explore the correlations between peripheral perfusion and mean arterial pressure and to investigate the correlations between peripheral perfusion and the dose of norepinephrine administered. Our hypotheses are that in the first hours of sepsis there was a correlation between MAP and peripheral perfusion and between the dose of norepinephrine administered and peripheral perfusion disorders.

Results

Studied population

Between June 2018 to May 2019, 57 patients were included in the study (a flowchart is presented in appendix). Baseline characteristics are given in Table 1. The primary infection sites were the abdomen (55%), the lungs (23%) and the urinary tracts (12%). Thirty-six patients (63%) were mechanically ventilated. The mean SOFA score was 12.3 (3.5) and the median of SAPS II score was 70 (50 – 82). In this cohort, only one patient had myocardial dysfunction and received epinephrine in adjunction of norepinephrine. The 14-days mortality rate was 26% and the 28-days mortality rate was 34%.

Associations between peripheral perfusion and mean arterial pressure

There were poor negative correlations between $(T_c - T_t)$ and MAP, $(T_c - T_i)$ and MAP. The results of the correlations are presented in table 2. Figure 1 illustrates the plots of significant correlations.

The probability of observing an abnormal CRT was greater when MAP decreases (OR = 0.93 [0.87 – 0.98], P = 0.02). The results of the generalized linear model are presented table 3.

Associations between peripheral perfusion and the dose-rate of norepinephrine administered

There were fair positive correlations between three temperature gradients (Tc – Tt, Tc – Ti, Tskindiff) and NE dose. There was no significant correlation between MAP and NE dose (table 4).

Comparison of correlations over time

Twenty-nine patients belonged to the group “<12h” and 28 patients to the group “12-24h”. The medians of the delay were respectively 6h (3h – 9h) and 17h15 (16h – 19h30). Tissue perfusion parameters and MAP as a function of group are shown in Figure 3. We observed no significant difference between groups.

There was no significant correlation between NE dose and peripheral perfusion in group “<12h”. In group “12-24h”, there were fair correlations between NE dose and mottling score (r = 0.50, P = 0.006), NE dose and (Tc-Tt) (r = 0.38, P = 0.04), NE dose and Tskindiff (r = 0.45, P = 0.02). There were also moderately strong correlations between NE dose and (Tc-Ti) (r = 0.51, P = 0.005) NE dose and CRT (r = 0.59, P = 0.001).

Prognostic value of the dose-rate of norepinephrine administered

The dose-rate of NE perfused at the time of tissue perfusion measurement was associated with 14-days mortality (OR = 1.21 [1.06 – 1.38], P = 0.006) and with 28-days mortality (OR = 1.17 [1.01 – 1.36], P = 0.04) independently of MAP (before the start of NE), SOFA score, age, and BMI.

There was no significant association between the outcome and the interaction effect between infused NE dose and temperature gradients for either (Tc-Tt), (Tc-Ti) or Tskindiff (Appendix).

Discussion

The objectives of the study were to explore the correlations between peripheral perfusion, mean arterial pressure and the administration of vasopressors. The main results were the presence of correlations between MAP and peripheral perfusion parameters, and between peripheral perfusion disorders and NE dose-rate. Nevertheless, MAP and NE dose-rate were not correlated here.

In the current study, peripheral perfusion was evaluated in the early phase of the course of septic shock. Peripheral perfusion parameters include mottling score, CRT and temperature gradients, which quantitatively or semi-quantitatively assess skin perfusion, which is considered as a non-vital perfusion^{18,19}. The fair correlations that were found between core-to-skin temperature gradients and MAP in the early stages of septic shock appear logical. The presence of cold extremities is a clinical sign of circulatory shock that is commonly described, but is not specific of this condition²⁰. The skin temperature is the resultant balance between the heat transport within the peripheral tissues by blood circulation and the heat loss to the environment. Previous studies have described the correlations that exist between cardiac output or MAP and cutaneous perfusion, evaluated by the temperature of the skin²⁰⁻²³. Initially, septic shock is associated with a circulatory failure often of multiple origins associating hypovolemia, vasoplegia and reduction of cardiac inotropy^{4,24}. In response to this hemodynamic failure, the body initiates compensatory mechanisms whose objectives are to maintain a good perfusion of the vital organs. These compensatory mechanisms involve the activation of the sympathetic neurohumoral response that is responsible for the release of epinephrine and norepinephrine. These vasoactive molecules induce a peripheral vasoconstriction of peripheral vessels, particularly in the cutaneous territory, which lacks autoregulation regarding its perfusion^{18,22,25}. Peripheral perfusion is thus particularly sensitive to hemodynamic failure, and the decreased of skin temperature induced by this failure may be

assessed with thermography. In addition, it should also be emphasized that in our study, only temperature gradients were correlated with MAP, surprisingly CRT and mottling score were not, although they are also clinical signs of cutaneous hypoperfusion.

The presence of correlations between peripheral perfusion and macrocirculation in the first 24h after the start of vasopressor was in accordance with literature data : correlations have been described between tissue oxygenation, evaluated by NIRS, and cardiac output²⁶ or arterial pressure²⁷. Trzeciak et coll.²⁸ have described correlations between microcirculatory flow and arterial pressure. Several studies have been performed to assess the impact of an increase in MAP on tissue perfusion in patients with septic shock. Two of these studies reported an increase in tissue perfusion associated with an increase in blood pressure: the first study assessed muscle perfusion and the second²⁹, skin perfusion of the knee. In the latter, Kazune et al described an improvement in skin perfusion in response to the increase in MAP of 20 mmHg³⁰. This result is in agreement with those of our studies which describe a correlation between MAP and skin perfusion evaluated by measuring temperature gradients.

However, other studies did not report similar correlations^{31,32} and the increase of MAP was not associated with a better tissue perfusion in the Edul et al study. These conflicting results emphasizes the complexity of the interactions between macrocirculation and peripheral perfusion. The disparity of these results is probably of multifactorial origin, with methodological causes (peripheral perfusion was not measured in the same way in each study) and patients related causes (there are disparities between the clinical evolution of patients, in particular concerning the delay between the onset of the shock and the measure). In our study, these correlations were moderate, most likely because the measurements were taken several times after the onset of shock and after the implementation of resuscitation manoeuvres. In addition, all the measurements were not carried out at the same time for every patient, thus inducing some discrepancies.

In this study, no correlation between MAP and the dose-rate of administration of norepinephrine was noticed. This observation is probably related to the high diversity of septic shock profiles: some patients need more vasopressors to maintain their arterial pressure secondary to vascular hyporesponsiveness³³.

In the current study, the dose-rate of NE infused was correlated with temperature gradients. Correlations were also present between NE dose and mottling score and CRT after at least 12 hours of NE infusion. Moreover, these correlations were more pronounced in patients who received a longer catecholamine treatment. These results suggest that the administration of vasopressors may contribute to the persistence of hypoperfusion in some patients. The results of an experimental study performed on pigs support this hypothesis. In this study, pigs were anesthetized, and NE infusions were performed to increase MAP to 100 mmHg. Peripheral perfusion was evaluated by calculating temperature gradients measured by infrared thermography, as in the current study. In these pigs, NE perfusion was associated with a significant drop in temperature gradients suggesting the presence of NE-induced peripheral perfusion disturbances²³.

Another hypothesis is that patients with more severe circulatory shock and more pronounced peripheral perfusion disorders required the administration of a large amount of vasopressor. There is little published data on studying the correlation between the amounts of norepinephrine administered and the presence of signs of peripheral hypoperfusion, such as increased CRT or temperature gradients. One study reports minor correlation, bordering on statistical significance ($r = -0.20$, $P = 0.05$), between toe-to-room temperature gradient and the dose-rate of NE administered in patients with severe sepsis or septic shock⁷. However, the nature of our study does not allow conclusions about the possible causal link between the administration of NE

and the presence of peripheral perfusion disorders. For this purpose, longitudinal data analysis would be very interesting.

Interestingly, in the current study, the dose-rate of administration of NE was associated with early and late mortality. This result is not original, as several studies have reported an increased mortality with large doses of NE given to patients with septic shock^{16,34,35}. Auchet et coll. have reported that the perfusion of a high dose of NE concomitantly to a SOFA score > 10 was strongly associated with mortality. They described a cut-off value of 0.75 µg/kg/min for NE perfusion as a predicting factor of mortality with a sensibility of 73% and a specificity of 75%. Similar associations have also been described in larger studies that included critical patients with non-septic circulatory shock^{36,37}.

Several limitations must be acknowledged for the current study. First, the trial was performed in a single ICU centre in a small sample size. The small sample size reduces the statistical power of the study and increases the risk of type I errors. Only two physicians performed the inclusions and the measures of temperature gradients with infrared thermography. Infrared thermography is a painless, non-ionizing, contact-free and easy to perform diagnostic imaging technique. This technology has been used in literature to measure skin temperature in shock contexts^{23,38-41} but its reproducibility should be further assessed. Second, the measurements of skin perfusion and the infrared pictures were taken within the first 24 hours of the shock with a median time of 13 [6-23] hours. There was therefore some heterogeneity in the time of inclusion: some of the patients were treated for a few hours, which may have dampened the severity of shock. Third, it would have been interesting to study the links between peripheral perfusion disorders, mortality and the total amount of NE administered. Unfortunately, this data could not be obtained. Only the dose-rate of the infusion of NE at the time of measurement was registered. It is for this reason that we decided to carry out the two groups of the study, on the assumption that the group "12-24h"

had probably received greater amount of NE. Another limitation of the study is the lack of information regarding cardiac function, SvO₂ and fluid administration (quantity of fluids, parameters that guided their administration). We acknowledge that these values and their evolution could have been interesting. However, this pragmatic study reflects a "real life" ICU with different practitioner using different methods to evaluate myocardial dysfunction and to evaluate filling response (static or dynamic markers). Finally, we did not follow the evolution of the parameters over time. It would have been interesting to see how peripheral perfusion parameters behave as a function of changes in the dose-rate of NE perfused.

In conclusion, this study reports correlations between MAP and peripheral perfusion parameters and between the dose-rate of administration of NE and the severity of peripheral perfusion disorders. Few on this subject were published in the literature. However, our study does not allow to conclude about this causal link between NE administration and the persistence of peripheral perfusion disorders. This study is an exploratory study, further study with more patients is required to confirm its results.

Methods

Ethics

This study was a retrospective analysis of data acquired prospectively. The protocol was approved by the ethics committee (Comité de Protection des Personnes, SUD-EST IV, Lyon, France, Ref L15-2013). The original project was an observational prospective study. Patients were included between June 2018 and May 2019, with an oral informed consent obtained from all participants or from close relatives when the person was unable to provide consent. All patients and family were

informed that data and pictures were collected anonymously and would be used for academic research, with the possibility to retract at any time.

Inclusion criteria

Patients included in the study were adults (>18 years) with septic shock receiving vasopressor for less than 24 hours. Septic shock was defined according to the latest international consensus definition: sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) \geq 65 mm Hg and having a serum lactate level $>$ 2 mmol/L ⁴².

Patient management

Patients were managed according to the local procedures adapted from international guidelines ¹⁵. Fluid resuscitation was administered at the discretion of the practitioner using static and dynamic markers to optimize volemia and cardiac output. Then, after optimization of the volemic status, if hypotension was persisting, norepinephrine (NE) was used to maintain a MAP above 65 mmHg. Cardiac output and macrocirculatory monitoring were performed by transthoracic echocardiography (Vivid S6, General Electric Healthcare®, Chicago, USA) or thermodilution calibrated pulse contour analysis (PiCCO, Getinge®, Getinge, Sweden). Clinical and demographic characteristics of the patients were recorded as mentioned thereafter.

Data recording

The following clinical characteristics were collected: age, sex, body mass index, diabetes, vascular surgery, cirrhosis, solid cancer, hematologic cancer, mechanical ventilation, vasopressor dose and primary site of infection.

The SOFA score, lactate measurement, and the Simplified Acute Physiology Score (SAPS) II score, a severity of disease classification system, were calculated with the worst values from the 24 first hours since inclusion.

Mean arterial pressure

Two MAP values were recorded in the study. The MAP value at the time of peripheral perfusion measurement and the MAP value at the time of shock, before the initiation of NE infusion. The latter was rated MAP (before the start of NE) when it was used in this study.

Peripheral perfusion assessment

Peripheral perfusion was evaluated by the following parameters: Capillary refill time (CRT), the mottling score and core-to-skin temperature gradients.

At inclusion, capillary refill time (CRT) and skin temperature measurement were performed by two physicians.

The CRT at the knee was measured by applying a firm pressure on the dorsomedial aspect of the knee of the patient using the finger of the physician for 15 seconds. The pressure applied was aimed to remove the blood at the tip of the physician nail (blanching under the nail). The time of return to the normal colour was recorded by a chronometer. The method and knee location of capillary refill time over the index location was chosen according to the results of a previous study⁶. This measure was done twice and only the longest time was further analyzed in this study. A CRT > 3s was considered as abnormal.

The presence and degree of mottling was evaluated with a mottling score calculated as described by Ait-Oufella et al⁵.

Temperature of the skin was measured in three regions of interest (ROI) by infrared thermography (IT): the forearm, the index finger and the hallux. The thermographic pictures of each site were performed with an infrared thermographic camera (FLIR-E4, FLIR Systems Inc, Wilsonville, Oregon, USA) that presented the following characteristics: detector type: uncooled microbolometer, infrared resolution: 80*60 pixels, spectral range: 7.5 – 13 μm , spatial resolution: 10.3 mrad, field of view (FOV): 55° x 43°, object temperature range: -20°C to + 250°C, noise equivalent temperature difference < 150 mk, thermal sensitivity < 0.15°C, accuracy: \pm 2%, minimum focus distance: 50 cm. The device was calibrated as recommended by the manufacturer. Images were treated with a dedicated software (Flirtools software®, FLIR Systems Inc, Wilsonville, Oregon, USA) to extract the mean temperature of the ROI. For the skin temperature at the forearm, the ROI was located midway between the wrist and the elbow. For the skin temperature at the toe (Tt), the ROI lied at the extremity of the hallux. For the skin temperature at the index (Ti), the ROI was the last phalanx of the index finger. The measure was taken on both the left and right sides. The core temperature was recorded with a tympanic (Genius 2 Accusystem®, Covidien, Dublin, Ireland) or a urinal probe. Five temperature gradients (TG) were calculated as follow:

- Tc – Tt: temperature of the toe subtracted from the core temperature
- Tc – Ti: temperature of the index subtracted from the core temperature
- Tskindiff: temperature of the index subtracted from temperature of the forearm, as described in the literature ⁴³

Only the highest gradient, whatever the side, was further analysed.

Norepinephrine administration

The dose-rate of norepinephrine administration (NE dose) at the time of tissue perfusion assessment was recorded.

The population was divided into two groups according to the delay between the initiation of NE perfusion and the time of measurement of peripheral perfusion parameters. In the group “<12h” this delay was inferior to 12 hours. In the group “12-24h” the delay was comprised between 12 hours and 24 hours (appendix).

Statistical analysis

The distribution of the quantitative variables was analysed graphically by realization of histograms and Q-Q plots. Variables with a normal distribution were presented as mean (standard deviation). Other quantitative variables were presented as median (interquartile range). Pearson correlations were calculated between peripheral perfusion related parameters and MAP and NE dose. Univariate generalized linear models were performed to test the association between the presence of mottling or the presence of an abnormal CRT and MAP. For this, models including MAP as fixed effect and individuals as random effect were computed for mottling (presence/absence) and for CRT (normal/abnormal). In order to evaluate the association between 14-days or 28-days mortality and the amount of NE administered, a logistic regression was computed, including NE dose-rate, MAP (before the start of NE), SOFA score, age and BMI as adjustment variables. Results were expressed with OR [IC95%] and their respective p-values. Statistical analysis was performed using R 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria). The packages “ggplot2”, “Lme4”, “Lmertest”, and “gridExtra” were used. A P-value lower than 0.05 was considered as significant.

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Tables

Table1. Clinical and demographic characteristics of the patients

Characteristics	n = 57
Age (year)	68.4 (14.6)
Sex	Female 47% - Male 53%
Body mass index (kg/m ²)	24.9 (5.2)
Primary site of infection, n (%)	
Abdomen	31 (55%)
Lung	13 (23%)
Urinary tract	7 (12%)
Soft tissue	3 (5%)
Other or unknown	3 (5%)
Mechanical ventilation n (%)	36 (63%)
SOFA score (AU)	12.3 (3.6)
SAPSII score (AU)	70 (50 – 82)
MAP (mmHg)	71 (66 – 80)
HR (bpm)	102 (17)
Lactate (mg/L)	4.5 (3.0 – 7.5)
Mottling score (AU)	1 (0 – 2)
Presence of mottling n (%)	32 (56%)
CRT (s)	4.2 (3.1 – 5.4)
Abnormal CRT n (%)	44 (77%)
Tc-Tt (°C)	9.9 (6.4 – 11.3)
Tc-Ti (°C)	6.2 (2.7 – 8.9)
Tskindiff (°C)	4.9 (2.0 – 6.5)
NE dose (µg/kg/min)	0.41 (0.2 – 0.9)

AU: arbitrary unit, MAP: mean arterial pressure, HR: heart rate, bpm: beat per minute, CRT: capillary refill time, Tc: core temperature, Tt: toe temperature, Ti: index temperature, Tskindiff: temperature of the index subtracted from temperature of the forearm, NE dose: dose-rate of norepinephrine perfusion administered.

Table 2. Correlations between mean arterial pressure and peripheral perfusion

		MAP
Mottling score	Pearson	-0.08
	correlation	
	P-value	0.54
CRT	Pearson	-0.21
	correlation	
	P-value	0.12
Tc-Tt	Pearson	-0.29
	correlation	
	P-value	0.03
Tc-Ti	Pearson	-0.27
	correlation	
	P-value	0.04
Tskindiff	Pearson	-0.12
	correlation	
	P-value	0.38

MAP: mean arterial pressure, CRT: capillary refill time, Tc: core temperature, Tt: toe temperature, Ti: index temperature.

Correlation coefficient interpretation: poor correlation $|r| < 0.30$, fair correlation $[0.30 \leq |r| < 0.50]$ - According to Chan YH

⁴⁴. Significant correlations are presented in bold type.

Table 3. Results of generalized linear models

		MAP
Presence of mottling	Odd ratio (estimate)	0.98 (-0.02)
	P-value	0.41
Abnormal CRT	Odd ratio (estimate)	0.93 (-0.07)
	P-value	0.02

MAP: mean arterial pressure. CRT: capillary refill time. Significant results are presented in bold type.

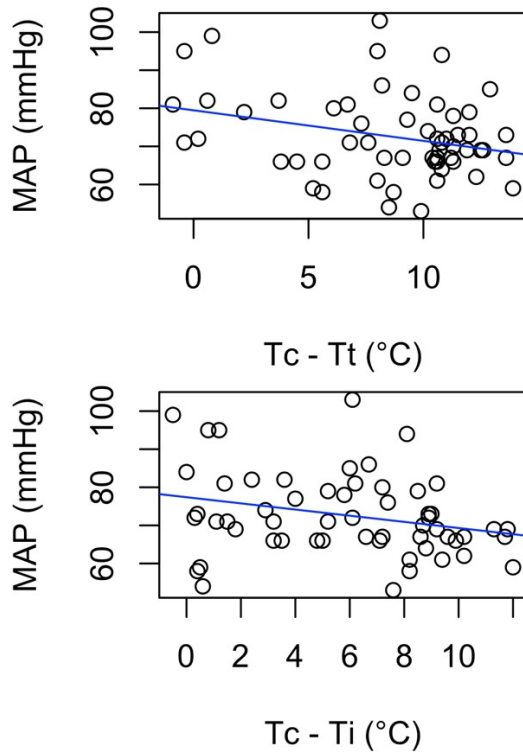
Table 4. Correlations between the dose-rate of norepinephrine administered and peripheral perfusion parameters

		NE dose
Mottling score	Pearson correlation	0.10
	P-value	0.21
CRT	Pearson correlation	0.25
	P-value	0.06
Tc-Tt	Pearson correlation	0.31
	P-value	0.02
Tc-Ti	Pearson correlation	0.34
	P-value	0.01
Tskindiff	Pearson correlation	0.35
	P-value	0.008
MAP	Pearson correlation	-0.20
	P-value	0.13

MAP: mean arterial pressure, CRT: capillary refill time, Tc: core temperature, Tt: toe temperature, Ti: index temperature, Tskindiff: temperature of the index subtracted from temperature of the forearm, NE dose: dose-rate of norepinephrine perfusion administered. Correlation coefficient interpretation: poor correlation $|r| < 0.30$, fair correlation $[0.30 \leq |r| < 0.50]$ - According to Chan YH⁴⁴. Significant correlations are presented in bold type.

Figure*Figure 1.*

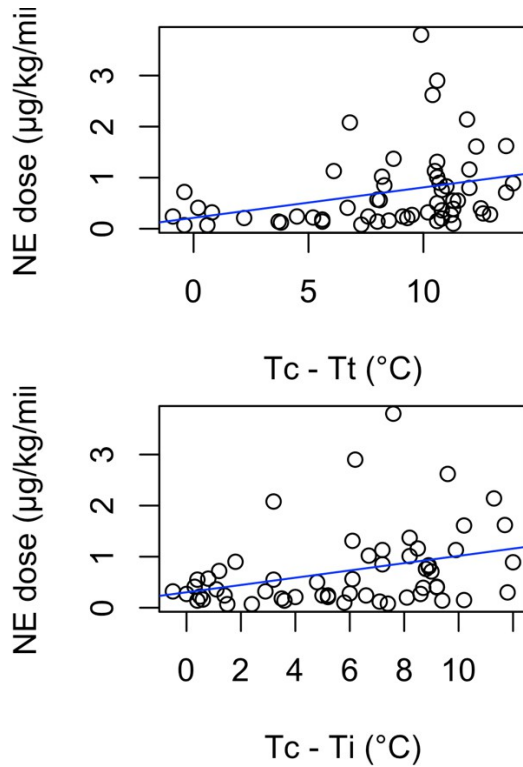
Plots corresponding to significant correlations between mean arterial pressure and peripheral perfusion parameters.



MAP: mean arterial pressure, bpm: beat per minute, CRT: capillary refill time, Tc: core temperature, Tt: toe temperature, Ti: index temperature.

Figure 2.

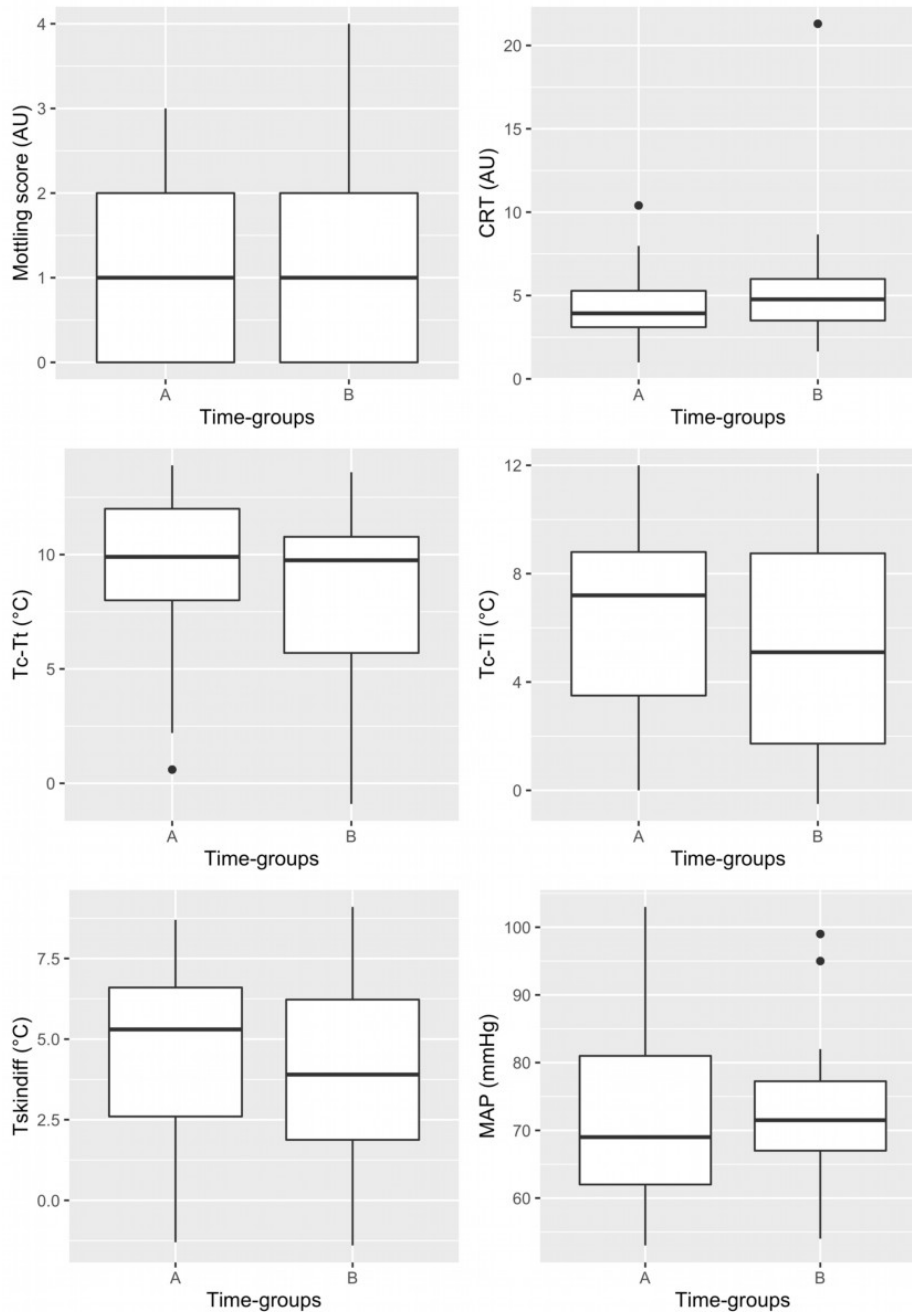
Plots corresponding to significant correlations between the dose-rate of norepinephrine administered and peripheral perfusion parameters.



Tc: core temperature, Tt: toe temperature, Ti: index temperature, Tskindiff: temperature of the index subtracted from temperature of the forearm, NE dose: dose-rate of norepinephrine administered.

Figure 3.

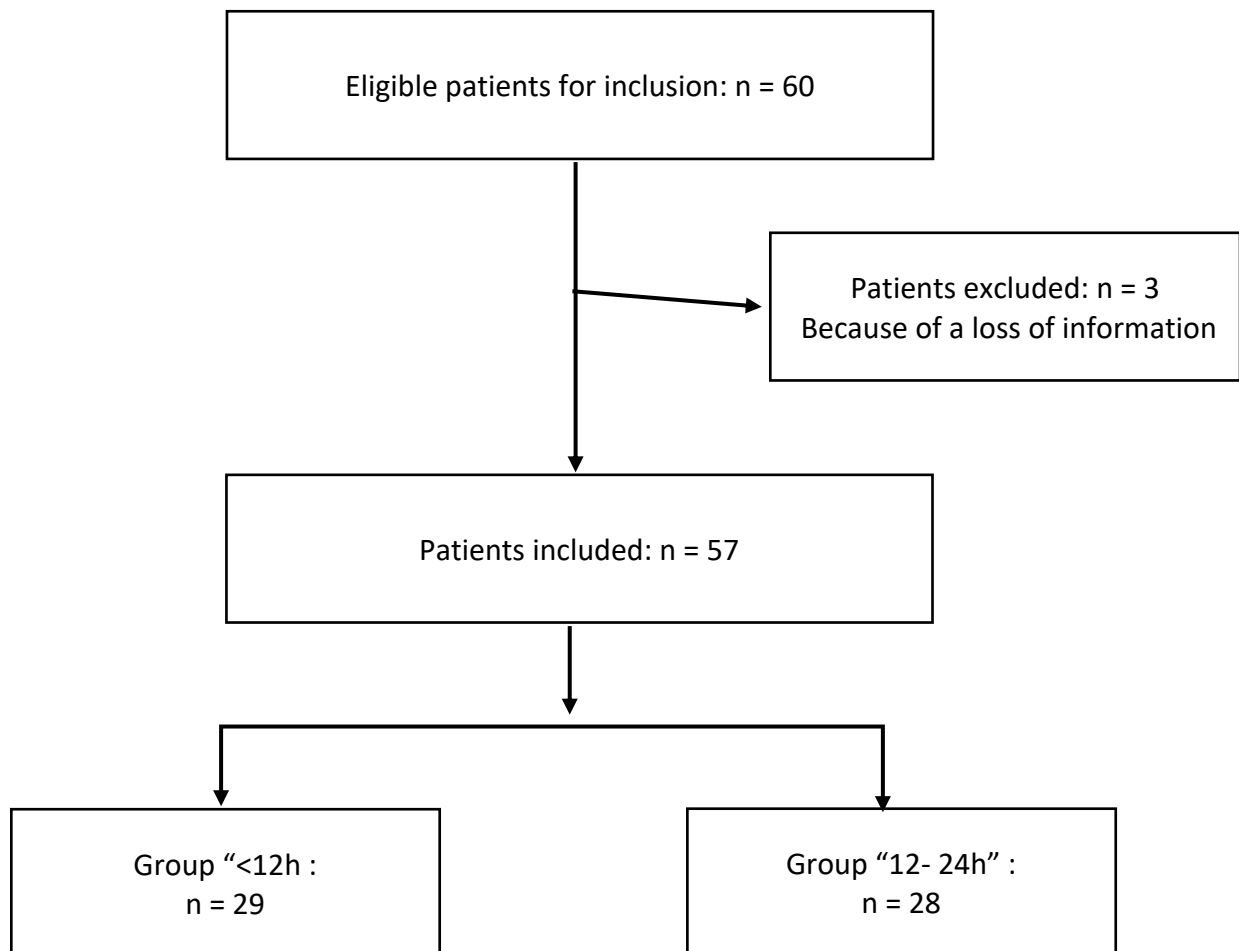
Title: Graphical presentation of peripheral perfusion parameters for the groups “<12h” and “12-24h”



A: group “<12h”, B: group “12-24h”, MAP: mean arterial pressure, HR: heart rate, CRT: capillary refill time, Tc: core temperature, Tt: toe temperature, Ti: index temperature, Tr: ambient room temperature - We observed no significant difference between groups.

Appendix.

- Flowchart of patient inclusion in the study



- Analysis of the association between interaction effect, between the dose of norepinephrine and temperature gradients, and outcome

Dependent variable	Independent variable	OR	CI95%	P
14-days mortality	NE dose	1.02	0.65 – 1.59	0.94
	Tc-Tt	0.99	0.95 – 1.03	0.76
	Interaction effect	1.02	0.97 – 1.06	0.44
14-days mortality	NE dose	1.21	0.84 – 1.74	0.30
	Tc-Ti	1.01	0.97 – 1.07	0.55
	Interaction effect	0.99	0.95 – 1.04	0.90
14-days mortality	NE dose	1.20	0.73 – 1.93	0.48
	Tskindiff	1.02	0.96 – 1.09	0.52
	Interaction effect	1.00	0.92 – 1.09	0.96
28-days mortality	NE dose	1.08	0.65 – 1.79	0.76
	Tc-Tt	1.00	0.96 – 1.05	0.92
	Interaction effect	1.01	0.96 – 1.06	0.77
28-days mortality	NE dose	1.23	0.82 – 1.86	0.32
	Tc-Ti	1.01	0.96 – 1.06	0.69
	Interaction effect	0.99	0.94 – 1.05	0.77
28-days mortality	NE dose	1.25	0.73 – 2.16	0.43
	Tskindiff	1.02	0.96 – 1.10	0.51
	Interaction effect	0.98	0.89 – 1.08	0.75

NE:

norepinephrine, OR: odd ratio, CI95%: 95% confidence interval, Tc: core temperature, Ti: index temperature, Tt: toe temperature