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Allaouchiche

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

Mathieu Magnin<sup>1,2\*</sup>, Harry Amson<sup>3,5</sup>, Charles-Hervé Vacheron<sup>3</sup>, Fabrice Thiollière<sup>3</sup>, Vincent Piriou<sup>3</sup>, Stéphane Junot<sup>1,6</sup>, Jeanne-Marie Bonnet Garin<sup>1,2</sup>, Bernard Allaouchiche<sup>1,3</sup>

<sup>1</sup> University of Lyon, APCSe Agressions Pulmonaires et Circulatoires dans le Sepsis (Pulmonary and circulatory disorders in sepsis), VetAgro Sup, 1 avenue Bourgelat F-69280 Marcy l'Etoile, France

<sup>2</sup> University of Lyon, VetAgro Sup, Physiology, 1 avenue Bourgelat F-69280 Marcy l'Etoile, France

<sup>3</sup> University of Lyon, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Intensive care unit, 165 Chemin du Grand Revoyet F-69310 Pierre-Bénite, France

<sup>4</sup>PHE3ID, Centre International de Recherche en Infectiologie, Institut National de la Santé et de la Recherche Médicale U1111, CNRS UMR 5308, Université Claude Bernard Lyon 1, France

<sup>5</sup> Hospices Civils de Lyon, Pôle Santé Publique, Service de Biostatistique - Bioinformatique, Lyon, France.

<sup>6</sup> University of Lyon, VetAgro Sup, Anesthesiology, 1 avenue Bourgelat F-69280 Marcy l'Etoile, France

\*corresponding author

Author for correspondence: Mathieu Magnin, [mathieu.magnin@vetagro-sup.fr](mailto:mathieu.magnin@vetagro-sup.fr), +33610014927, 1 avenue Bourgelat, 69280 Marcy L'Etoile, France

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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%.<sup>1,2</sup> 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<sup>3,4</sup>.

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 score<sup>5</sup>, capillary refill time (CRT)<sup>6</sup> and temperature gradients<sup>7</sup> are associated with mortality. In addition, it appears that tissue perfusion disorders is associated with the presence of organ failure<sup>7-9</sup>. 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<sup>4,10</sup>. Therefore, they suggest that peripheral perfusion parameters should be used as objectives to guide therapeutic management<sup>11-13</sup>. 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 administered<sup>14</sup>. 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 normalization<sup>12</sup>. Mean arterial pressure (MAP) is one of the parameters conventionally used to guide the resuscitation of patients today<sup>15</sup>. 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<sup>16,17</sup>, 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<sup>18,19</sup>. 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 condition<sup>20</sup>. 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 skin<sup>20-23</sup>. Initially, septic shock is associated with a circulatory failure often of multiple origins associating hypovolemia, vasoplegia and reduction of cardiac inotropy<sup>4,24</sup>. 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<sup>18,22,25</sup>. 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 output<sup>26</sup> or arterial pressure<sup>27</sup>. Trzeciak et coll.<sup>28</sup> 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 second<sup>29</sup>, 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 mmHg<sup>30</sup>. 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<sup>31,32</sup> 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 hyporesponsiveness<sup>33</sup>.

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 disturbances<sup>23</sup>.

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 shock<sup>7</sup>. 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<sup>16,34,35</sup>. 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<sup>36,37</sup>.

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<sup>23,38-41</sup> 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, SvO<sub>2</sub> 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 <sup>42</sup>.

#### *Patient management*

Patients were managed according to the local procedures adapted from international guidelines <sup>15</sup>. 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 study<sup>6</sup>. 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 al<sup>5</sup>.

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  $\mu\text{m}$ , 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 (Flirttools 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 <sup>43</sup>

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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## References

1. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. *Crit Care*. 2020 May 19;24(1):239.
2. Vincent J-L, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. *Crit Care Lond Engl*. 2019 May 31;23(1):196.
3. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *The Lancet*. 2018 Jul 7;392(10141):75–87.
4. Hernandez G, Bruhn A, Castro R, Regueira T. The holistic view on perfusion monitoring in septic shock: *Curr Opin Crit Care*. 2012 Jun;18(3):280–6.
5. Ait-Oufella H, Lemoine S, Boelle PY, Galbois A, Baudel JL, Lemant J, et al. Mottling score predicts survival in septic shock. *Intensive Care Med*. 2011 May;37(5):801–7.
6. Ait-Oufella H, Bige N, Boelle PY, Pichereau C, Alves M, Bertinchamp R, et al. Capillary refill time exploration during septic shock. *Intensive Care Med*. 2014 Jul;40(7):958–64.
7. Bourcier S, Pichereau C, Boelle P-Y, Nemlaghi S, Dubée V, Lejour G, et al. Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. *Ann Intensive Care*. 2016 Dec;6(1):63.
8. Hernandez G, Boerma EC, Dubin A, Bruhn A, Koopmans M, Edul VK, et al. Severe abnormalities in microvascular perfused vessel density are associated to organ dysfunctions and mortality and can be predicted by hyperlactatemia and norepinephrine requirements in septic shock patients. *J Crit Care*. 2013 Aug;28(4):538.e9-14.
9. Sakr Y, Dubois M-J, De Backer D, Creteur J, Vincent J-L. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004 Sep;32(9):1825–31.
10. Gazmuri RJ, de Gomez CA. From a pressure-guided to a perfusion-centered resuscitation strategy in septic shock: Critical literature review and illustrative case. *J Crit Care*. 2020 Apr 1;56:294–304.
11. Hernandez G, Pedreros C, Veas E, Bruhn A, Romero C, Rovegno M, et al. Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation. A clinical-physiologic study. *J Crit Care*. 2012 Jun 1;27(3):283–8.
12. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA*. 2019 Feb 19;321(7):654–64.
13. van Genderen ME, Engels N, van der Valk RJP, Lima A, Klijn E, Bakker J, et al. Early Peripheral Perfusion–guided Fluid Therapy in Patients with Septic Shock. *Am J Respir Crit Care Med*. 2015 Feb 15;191(4):477–80.
14. van Genderen ME, Engels N, van der Valk RJP, Lima A, Klijn E, Bakker J, et al. Early Peripheral Perfusion–guided Fluid Therapy in Patients with Septic Shock. *Am J Respir Crit Care Med*. 2015 Feb 13;191(4):477–80.
15. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017 Mar;43(3):304–77.
16. Achet T, Regnier M-A, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. *Ann Intensive Care*. 2017 Dec;7(1):43.



17. Hayes MA, Yau EH, Hinds CJ, Watson JD. Symmetrical peripheral gangrene: association with noradrenaline administration. *Intensive Care Med.* 1992;18(7):433–6.
18. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. *Intensive Care Med.* 2005 Oct 1;31(10):1316–26.
19. Lima A, Bakker J. Clinical monitoring of peripheral perfusion: there is more to learn. *Crit Care.* 2014;18(1):113.
20. Joly HR. Temperature of the Great Toe as an Indication of the Severity of Shock. 1969;8.
21. Love TJ. Thermography as an Indicator of Blood Perfusion. *Ann N Y Acad Sci.* 1980;335(1):429–37.
22. Felder D, Russ E, Montgomery H, Horwitz O. Relationship in the toe of skin surface temperature to mean blood flow measured with a plethysmograph. *Clin Sci.* 1954 May;13(2):251–6.
23. Magnin M, Junot S, Cardinali M, Ayoub J-Y, Paquet C, Louzier V, et al. Use of infrared thermography to detect early alterations of peripheral perfusion -Evaluation in a porcine model. *Biomed Opt Express.* 2020 Mar;11:2431-46.
24. Russell JA, Rush B, Boyd J. Pathophysiology of Septic Shock. *Crit Care Clin.* 2018 Jan 1;34(1):43–61.
25. Schey BM, Williams DY, Bucknall T. Skin temperature and core-peripheral temperature gradient as markers of hemodynamic status in critically ill patients: a review. *Heart Lung J Crit Care.* 2010 Feb;39(1):27–40.
26. Payen D, Luengo C, Heyer L, Resche-Rigon M, Kerever S, Damoiseil C, et al. Is thenar tissue hemoglobin oxygen saturation in septic shock related to macrohemodynamic variables and outcome? *Crit Care.* 2009;13(Suppl 5):S6.
27. Collet M, Huot B, Barthélémy R, Damoiseil C, Payen D, Mebazaa A, et al. Influence of systemic hemodynamics on microcirculation during sepsis. *J Crit Care.* 2019 Aug;52:213–8.
28. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med.* 2007 Jan 1;49(1):88-98.e2.
29. Thooft A, Favory R, Salgado DR, Taccone FS, Donadello K, De Backer D, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care Lond Engl.* 2011;15(5):R222.
30. Kazune S, Caica A, Luksevics E, Volceka K, Grabovskis A. Impact of increased mean arterial pressure on skin microcirculatory oxygenation in vasopressor-requiring septic patients: an interventional study. *Ann Intensive Care.* 2019 Aug 29;9(1):97.
31. Backer DD, Donadello K, Sakr Y, Ospina-tascon G, Salgado D, Scolletta S, et al. Microcirculatory Alterations in Patients With Severe Sepsis: Impact of Time of Assessment and Relationship With Outcome\*. *Crit Care Med.* 2013 Mar 1;41(3):791–9.
32. Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. *Arch Dis Child.* 1999 Feb;80(2):163–6.
33. A K, N D, B L. Mechanisms of vascular hyporesponsiveness in septic shock. *Curr Vasc Pharmacol.* 2013 Mar 1;11(2):139–49.
34. Jenkins CR, Gomersall CD, Leung P, Joynt GM. Outcome of Patients Receiving High Dose Vasopressor Therapy: A Retrospective Cohort Study. *Anaesth Intensive Care.* 2009 Mar 1;37(2):286–9.
35. Domizi R, Calcinaro S, Harris S, Beilstein C, Boerma C, Chiche J-D, et al. Relationship

- between norepinephrine dose, tachycardia and outcome in septic shock: A multicentre evaluation. *J Crit Care*. 2020 Jun 1;57:185–90.
36. Döpp-Zemel D, Groeneveld ABJ. High-dose norepinephrine treatment: determinants of mortality and futility in critically ill patients. *Am J Crit Care Off Publ Am Assoc Crit-Care Nurses*. 2013 Jan;22(1):22–32.
  37. Benbenishty J, Weissman C, Sprung CL, Brodsky-Israeli M, Weiss Y. Characteristics of patients receiving vasopressors. *Heart Lung J Crit Care*. 2011 Jun;40(3):247–52.
  38. Ferraris A, Bouisse C, Mottard N, Thiollière F, Anselin S, Piriou V, et al. Mottling score and skin temperature in septic shock: Relation and impact on prognosis in ICU. *PLoS ONE*. 2018 Aug;13(8). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6095547/>
  39. Łokaj M, Czapla N, Falkowski A, Prowans P. The use of thermography in early detection of tissue perfusion disorders in rats. *Videosurgery Miniinvasive Tech*. 2014 Sep;9(3):329–36.
  40. Ortiz-Dosal A, Kolosovas-Machuca ES, Rivera-Vega R, Simón J, González FJ. Use of infrared thermography in children with shock: A case series. *SAGE Open Med Case Rep*. 2014 Dec;2. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4857355/>
  41. Pereira CB, Czaplik M, Blanik N, Rossaint R, Blazek V, Leonhardt S. Contact-free monitoring of circulation and perfusion dynamics based on the analysis of thermal imagery. *Biomed Opt Express*. 2014 Mar 5;5(4):1075–89.
  42. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016 Feb 23;315(8):801–10.
  43. van Genderen ME, van Bommel J, Lima A. Monitoring peripheral perfusion in critically ill patients at the bedside. *Curr Opin Crit Care*. 2012 Jun;18(3):273–9.
  44. Chan YH, B B, Chan YH, Biostatistics HO, Chan YH. Vaccine Clinical Trials. In: in *Encyclopedia of Biopharmaceutical Statistics*, 2nd Edition, Marcel Dekker. 2003. p. 1005–22.

## 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 <sup>2</sup> )	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

<sup>44</sup>. Significant correlations are presented in bold type.

Table 3. Results of generalized linear models

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

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

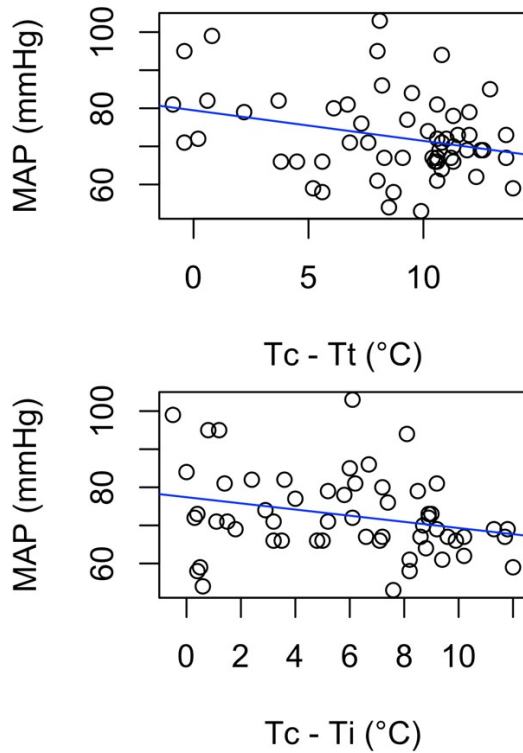
Table 4. Correlations between the dose-rate of norepinephrine administered and peripheral perfusion parameters

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

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 YH<sup>44</sup>. Significant correlations are presented in bold type.

**Figure***Figure 1.*

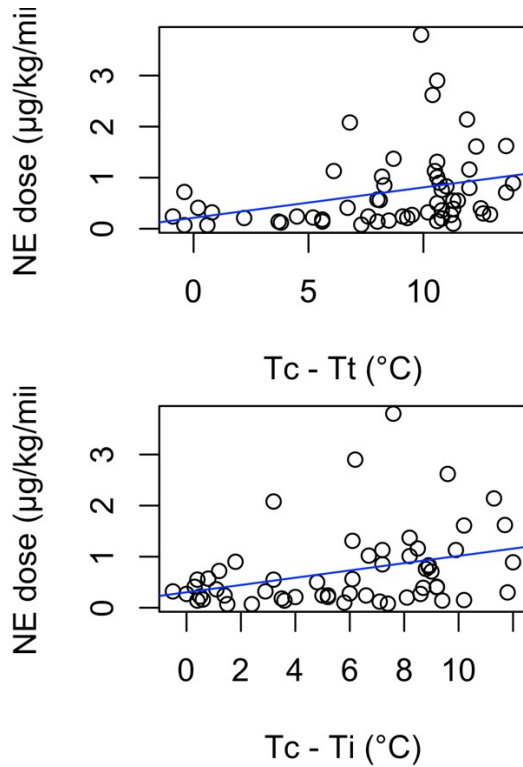
Plots corresponding to significant correlations between mean arterial pressure and peripheral perfusion parameters.



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.

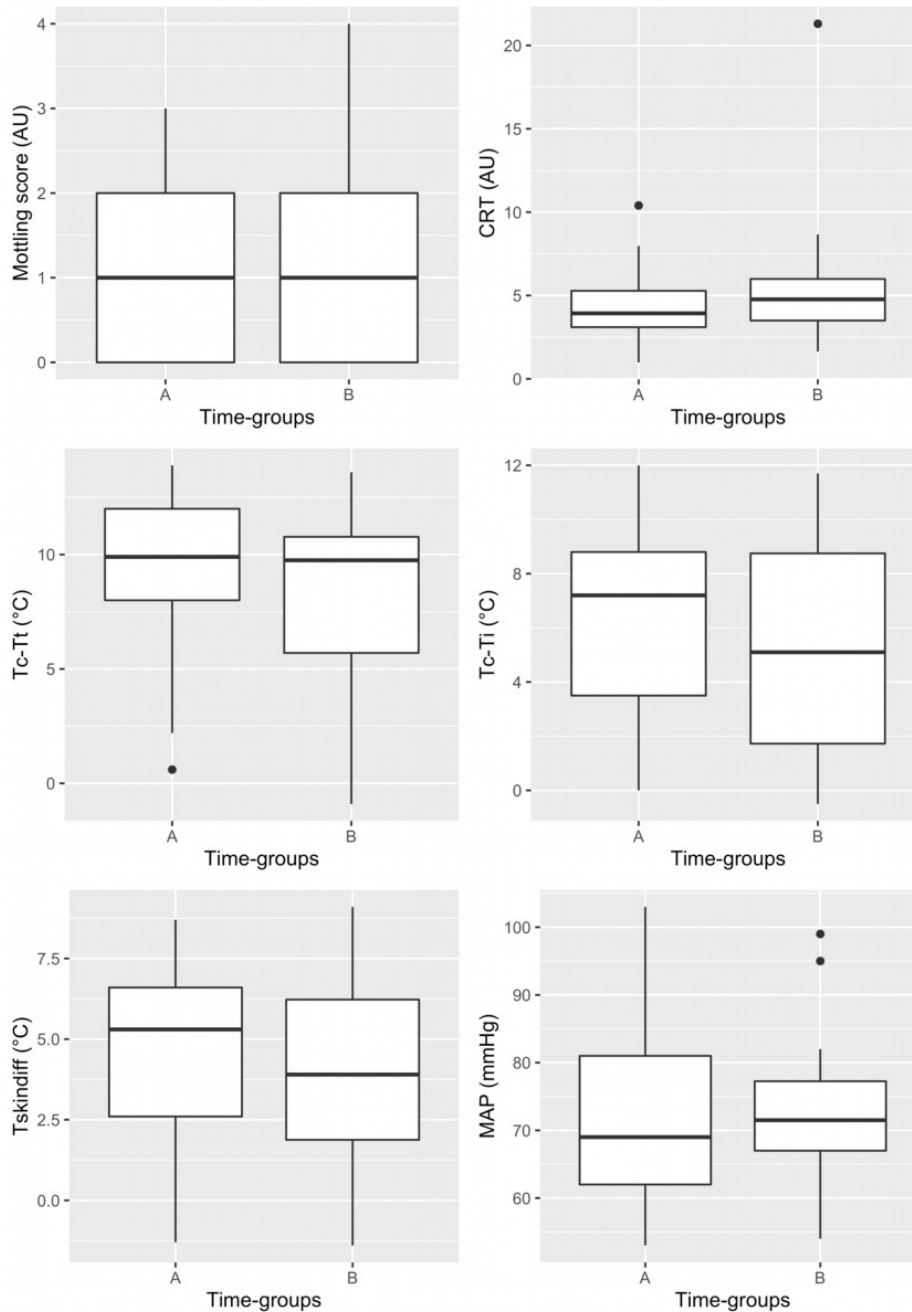


Tc: core temperature, Tt: toe temperature, Ti: index temperature, Tskindiff: temperature of the index subtracted from temperature of the forearm, NE dose: dose-rate of norepinephrine administered.



Figure 3.

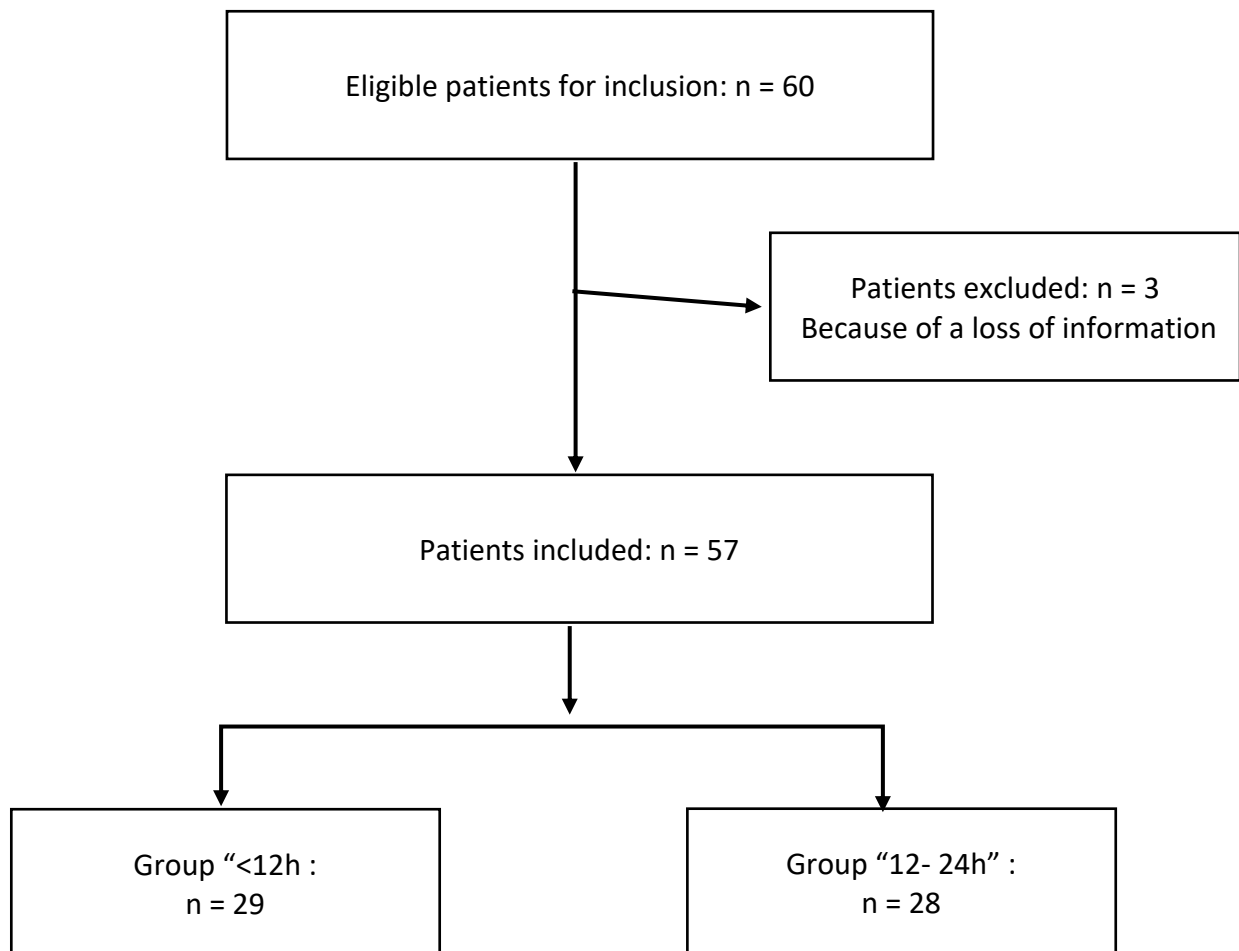
Title: Graphical presentation of peripheral perfusion parameters for the groups “<12h” and “12-24h”



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