Journal of Intensive Medicine 2 (2022) 17–21

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

The role of peripheral perfusion markers and lactate in septic shock resuscitation

Eduardo Kattan, Glenn Hernández*

Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad de Chile, Santiago 7500000, Chile

ARTICLE INFO

Keywords:
Septic shock
Lactate
Capillary refill time

ABSTRACT

Septic shock leads to progressive hypoperfusion and tissue hypoxia. Unfortunately, numerous uncertainties exist around the best monitoring strategy, as available techniques are mere surrogates for these phenomena. Nevertheless, central venous oxygen saturation ($ScvO_2$), venous-to-arterial CO_2 gap, and lactate normalization have been fostered as resuscitation targets for septic shock. Moreover, recent evidence has challenged the central role of lactate. Following the ANDROMEDA-SHOCK trial, capillary refill time (CRT) has become a promissory target, considering the observed benefits in mortality, treatment intensity, and organ dysfunction. Interpretation of CRT within a multimodal approach may aid clinicians in guiding resuscitative interventions and stop resuscitation earlier, thus avoiding the risk of morbid fluid overload. Integrative assessment of a patient's perfusion status can be easily performed using bedside clinical tools. Based on its fast kinetics and recent supporting evidence, targeting CRT (within a holistic assessment of perfusion) may improve outcomes in septic shock resuscitation.

Introduction

Septic shock is associated with a high risk of mortality related to progressive tissue hypoperfusion.[1] However, despite extensive researches on the best monitoring and resuscitation strategies, numerous uncertainties remain. Over-resuscitation, particularly when inducing fluid overload, may contribute to a worse outcome.[2] Fluid overload occurs more likely when: (1) fluids are administered to fluid unresponsive patients; (2) inappropriate resuscitation goals are pursued; and (3) a "one-size-fits-all" strategy is followed.[3]

A top priority in septic shock resuscitation is to recognize hypoperfusion in early stages before the development of generalized tissue hypoxia. Therefore, it has been proposed that several perfusion-related markers, such as lactate,[4] central venous oxygen saturation ($ScvO_2$),[5] venous-to-arterial CO_2 gap,[6] and peripheral perfusion,[7] can be utilized to indirectly monitor the status of tissue perfusion and/or hypoxia. However, their potential role has broadened over time to areas not strictly related to the original physiological significance. Indeed, perfusion-related variables have been used as triggers or targets in septic shock resuscitation.[8] prognostic markers,[9,10] surrogates of cardiac output.[6] signals of underlying microcirculatory alterations.[11] etc.

The purpose of this article is to review the currently available literature on perfusion monitoring in septic shock and provide some integrative insight into this field, particularly following the ANDROMEDA-SHOCK trial.[8]

Complexities in the Interpretation of Perfusion-related Variables

Despite advances in knowledge regarding pathogenic mechanisms and numerous studies performed in the last decades, many uncertainties on perfusion monitoring in patients with septic shock persist.

First, tissue hypoxia (the ultimate consequence of shock) is a cellular/mitochondrial phenomenon poorly captured by systemic or metabolic variables, which can only be considered as surrogates or approximations to the events occurring at the tissue level.[12]

Second, tissues may be heterogeneously affected by hypoperfusion, and the hepatosplanchnic region (one of the most relevant territories) may be considered a "black box" in terms of

* Corresponding author: Glenn Hernández
E-mail address: glennguru@gmail.com (G. Hernández).

https://doi.org/10.1016/j.jointm.2021.11.002
Received 13 August 2021; Received in revised form 4 November 2021; Accepted 18 November 2021. Managing Editor: Jingling Bao
Available online 21 December 2021

perfusion monitoring; moreover, advances in regional flow assessment are scarce.[13]

Third, sublingual microcirculatory evaluation has not been applied to routine clinical practice and remains in the research phase.[14] Technical aspects, logistics, costs, and lack of agreement between experts on the most appropriate approach to capturing and analyzing images may have compromised further development.

Finally, it is impossible to consider a single parameter as the hallmark for monitoring tissue perfusion or guiding septic shock resuscitation due to the complexity of sepsis-related acute circulatory dysfunction.[15] All individual parameters have limitations and interpretation difficulties, rendering the multimodal monitoring of perfusion imperative.[16]

Definitions of Septic Shock

Current definitions of septic shock have inherent limitations because some are predominately focused on pathophysiological concepts. For example, the definition proposed by the hemodynamic consensus of the European Society of Intensive Care Medicine is as follows: "Shock is best defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells".[17]] Although this approach is relevant, it does not provide information on how to translate the pathophysiological term dysoxia into clinical variables.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) provide a more clinically-oriented definition of septic shock. Nevertheless, this definition has been criticized because it does not consider that lactate is a non-specific marker of tissue hypoperfusion.[18] Data from several previous studies suggest that interpretation of hyperlactatemia is conditioned by the hypoperfusion context.[15,19] Patients without a hypoperfusion context may be at a low risk of mortality and could be harmed by over-resuscitation when pursuing lactate normalization as a goal.[20]

None of the definitions captures the early stages of sepsis-related acute circulatory dysfunction as they are based on patients with volume-refractory hypotension requiring treatment with vasopressors.[18,21] However, in earlier stages, patients may arrive at the emergency department (ED) with a hyperadrenergic compensatory state without evident hypotension, and marked tachycardia and peripheral vasoconstriction. Clinicians who are unaware of these early signs may miss the diagnosis at a stage in which hypoperfusion is easily reversible.

Hemodynamic Coherence

The pathogenic mechanisms involved in sepsis-related acute circulatory dysfunction change over time. This process includes a transition from loss of vascular tone and relative hypovolemia in early stages (dry microcirculation) to progressive endothelial and coagulation dysfunction with severe derangements at the microcirculatory level in an advanced stage (inflamed microcirculation).[22] This transition may not be easily recognizable, particularly when patients are assessed at a single time-point. However, it is relevant since it is the basis for the concept of hemodynamic coherence.[22–24] Indeed, in the early stage, increasing systemic blood flow or perfusion pressure may improve tissue hypoperfusion since macrocirculation and microcirculation are coupled. In contrast, increasing cardiac output with fluids in the later stage may not improve microcirculatory flow. In fact, this may worsen derangements by inducing fluid overload and venous congestion after the loss of hemodynamic coherence. Thus, this concept should be considered in the interpretation of perfusion monitoring.[25]

Peripheral Perfusion

The pathophysiological determinants and technical aspects of peripheral perfusion assessment have been extensively discussed in contemporary literature.[26–29] Capillary refill time (CRT) and the mottling score.[26,27,29,30] have been incorporated into routine clinical monitoring worldwide. This incorporation was based on solid observational data, which established the prognostic value of these parameters.[8,11,31] Patients with normal peripheral perfusion after initial or advanced septic shock resuscitation were at a lower risk of mortality in several contexts (absolute difference in risk: 20–25%) compared with those who exhibited persistent abnormal CRT or mottling.[11,31,32] This difference is striking and may simply represent the impact of underlying hemodynamic coherence, where rapid normalizers are probably in the early stages of circulatory dysfunction and, therefore, highly responsive to flow-increasing maneuvers (e.g., with fluids in fluid-responsive patients).[23,25] In contrast, the phenotype of CRT-non-responders may reflect hemodynamic uncoupling and a more advanced stage. For such cases, rescue or immunomodulatory therapies may be considered earlier in the process.[23,33]

The ANDROMEDA-SHOCK Trial

The ANDROMEDA-SHOCK trial was a multicenter, randomized, controlled study comparing CRT- *vs.* lactate-targeted resuscitation in 424 patients with early septic shock.[8,34,35] According to the hypothesis, targeting of CRT leads to decreased mortality and organ dysfunction. The rationale behind this hypothesis is that CRT is a flow-sensitive variable that can be assessed at very frequent intervals (30 min) compared with lactate. The latter exhibits relatively slow kinetics of recovery in some patients due to delayed metabolic clearance. This could theoretically allow earlier termination of resuscitation when a CRT target is pursued. This fact may decrease the risk of over-resuscitation and eventually mortality and organ dysfunction.[8]

In the study, CRT was assessed using a novel standardized technique to improve interrater reliability. The intervention period was 8 h, and resuscitation goals were a normal CRT (≤3 s) *vs.* a normalization or decrease >20% in the levels of lactate. The protocol mandated sequential steps commencing with fluid challenges, followed by vasoactive-related interventions if necessary, until the target was reached.

Compared with lactate-targeted resuscitation, CRT-targeted resuscitation was associated with a trend toward lower 28-day mortality rate (43.4% *vs.* 34.9%, respectively; P=0.060), less organ dysfunction at 72 h (P = 0.045), lower mortality in the predefined subgroup of patients with less organ dysfunctions at baseline (39.3% *vs.* 20.4%, respectively; P=0.030), faster improvement in organ dysfunctions during the first 72 h (P<0.001), less resuscitation fluids (P=0.010), and less vaso-

pressor testing (P=0.020).[8] A subsequent Bayesian *post-hoc* analysis supported the survival benefit of CRT-targeted resuscitation.[36]

Perspectives Following the ANDROMEDA-SHOCK Trial

The ANDROMEDA-SHOCK trial was not designed as a mechanistic study; hence, many questions remain unsolved. A fundamental question is whether both strategies are equivalent in terms of improvement in tissue hypoperfusion or hypoxia-related parameters. Brunauer et al.[27] found a significant correlation between changes in CRT and mottling score with the pulsatility index of various hepatosplanchnic arteries during septic shock resuscitation. This correlation is physiologically coherent since both territories are affected by the same adrenergic response to circulatory stress that could be reverted at least partially by increments in systemic flow. A posterior clinical-physiological study demonstrated that normalization of CRT after fluid resuscitation is associated with comparable improvement in hypoxia surrogates and regional/microcirculatory blood flow to those observed with lactate; however, it is also linked to a faster achievement of target in CRT-guided resuscitation.[37]

Unfortunately, the complexity of the ANDROMEDA-SHOCK study protocol has limited its applicability to pre-intensive care unit (pre-ICU) settings. However, since CRT is a simple and universally available technique, more studies should be performed to establish its potential role in guiding septic shock resuscitation in EDs or resource-limited settings. Encouragingly, a couple of studies demonstrated the strong prognostic value of CRT after pre-hospital initial assessment[32] and following the first fluid resuscitation at the ED.[38] Eventually, the response of CRT to initial fluid resuscitation may be used for triage decisions, where non-responders should be rapidly transferred to the ICU for advanced monitoring and treatment. The potential usefulness of newly developed optical devices to objectively assess CRT.[39,40] and further establish its role as a dynamic cardiovascular test is also being investigated.[28]

Lactate

The strong prognostic value of persistent hyperlactatemia is undebatable. However, there is still some discussion concerning the correct terminology (delta *vs.* clearance) for the definition of lactate reduction in response to resuscitation in the ICU.[9,10,26,41] To be rigorous, the term clearance should be abandoned since the evolution of lactate levels over time reflects the balance between increased production, redistribution, and metabolism in shock states, and not only real clearance in kinetic terms.[20]

A slow decrease is frequently associated with a worse prognosis; nonetheless, caution should be exercised since this also depends on the hypoperfusion context.[15,19,20,42] In a retrospective proof-of-concept study, patients with hyperlactatemia but normal $ScvO_2$, venous-to-arterial CO_2 gap, and CRT (e.g., more flow-sensitive variables) demonstrated less severe circulatory dysfunction with lower requirement for norepinephrine, and a trend toward shorter ICU length of stay, less rescue therapies, and lower mortality rate *vs.* those with abnormal $ScvO_2$, venous-to-arterial CO_2 gap, and CRT.[15] Serum lactate levels remain elevated in half of septic shock survivors 24 h after initiating ICU-based resuscitation. In contrast, the more flow-sensitive variables return within the normal range in 70–80% of patients after only 2 h.[19]

In the ANDROMEDA-SHOCK trial, all patients fulfilled the Sepsis-3 definition of septic shock, which includes hyperlactatemia as an obligatory criterion.[8] In a *post-hoc* analysis, 25% of the global cohort had a normal CRT at baseline. These patients exhibited a significant lower mortality rate than those with an abnormal baseline CRT, regardless of the group in which they were allocated (27% *vs.* 43%, respectively; P=0.001). This finding was confirmed by a multivariate analysis where abnormal CRT at baseline was an independent determinant of 28-day mortality (odds ratio: 1.8; 95% confidence interval: 1.07–3.02; P=0.026).[43]] These data challenge one of the proclaimed objectives of the Sepsis-3 definition of septic shock, which is to identify a cohort of patients at similar risk of death.[18] In addition, they support that hyperlactatemia should always be interpreted under the perspective of the hypoperfusion context.

These data redetermine the role of lactate in septic shock resuscitation. Several experts have recently emphasized the pitfalls of lactate clearance as a potential target in septic shock resuscitation based on several considerations. This is particularly attributed to the fact that, in most cases, the main source of hyperlactatemia is not residual hypoperfusion or hypoxia, but rather stress-related hyperlactatemia.[20,44] Considering the risk of over-resuscitation, this condition should not be treated with further resuscitation or the "lacto-bolo reflex".[45] Data from the ANDROMEDA-SHOCK trial tend to support this principle.[8] In addition, results from another *post-hoc* analysis of the ANDROMEDA-SHOCK trial suggest that pursuing a lactate target in patients with already normal CRT at 2 h may increase the mortality rate.[46]

Nevertheless, changes in lactate level may provide valuable information on the course of septic shock resuscitation. A failure to decrease the levels of lactate should lead to a reevaluation

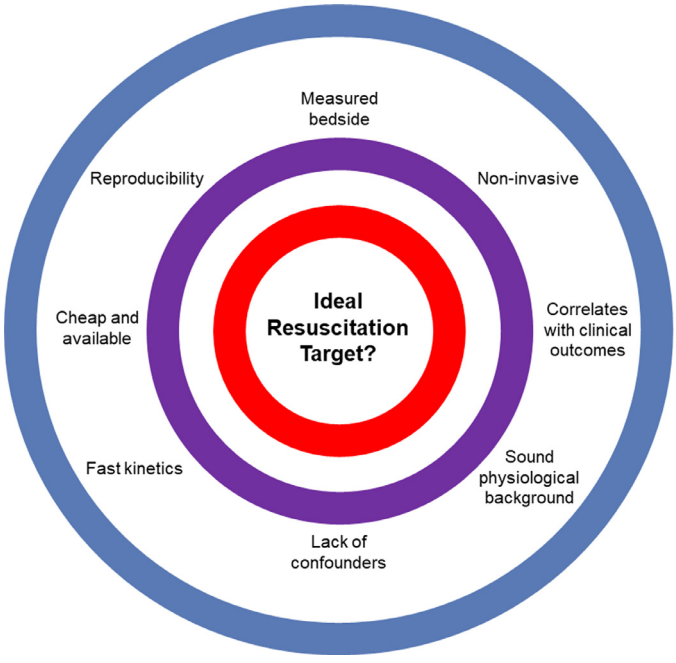

Figure 1. Characteristics of the ideal resuscitation target.

of the diagnosis, source control, and hemodynamic/perfusion status.

Relevance of Target Selection in Avoiding Fluid Overload

Based on the available literature, it is evident that perfusion-related variables have different pathophysiological determinants and kinetics of recovery after successful resuscitation. Pursuing a rapid-response or targeting more flow-sensitive variables, such as CRT, may allow earlier termination of the resuscitative process, thereby eventually avoiding the risk of fluid overload [Figure 1].

Conclusions

The importance of CRT and lactate is supported by robust physiological and epidemiological findings. Moreover, complexities in their interpretation and potential confounders warrant a multimodal approach to assessing the perfusion status. Considering its fast kinetics and the recent results of a major randomized clinical trial, CRT could be considered a hierarchical perfusion variable and serve as a resuscitation target for septic shock resuscitation.

Funding

This work was supported by the FONDECYT-ANID [Grant No. 1200246].

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

[1] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392(10141):75–87. doi:10.1016/S0140-6736(18)30696-2.
[2] Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39(2):259–65. doi:10.1097/CCM.0b013e3181feeb15.
[3] 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;43(3):304–77. doi:10.1007/s00134-017-4683-6.
[4] Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010;182(6):752–61. doi:10.1164/rccm.200912-1918OC.
[5] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77. doi:10.1056/NEJMoa010307.
[6] Gavelli F, Teboul JL, Monnet X. How can CO2-derived indices guide resuscitation in critically ill patients. J Thorac Dis 2019;11(Suppl 11):S1528–37. doi:10.21037/jtd.2019.07.10.
[7] 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;40(7):958–64. doi:10.1007/s00134-014-3326-4.
[8] 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;321(7):654–64. doi:10.1001/jama.2019.0071.
[9] Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the surviving sepsis campaign database. Crit Care Med 2015;43(3):567–73. doi:10.1097/CCM.0000000000000742.
[10] Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med 2016;42(2):202–10. doi:10.1007/s00134-015-4127-0.
[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;27(3):283–8. doi:10.1016/j.jcrc.2011.05.024.
[12] MacIntyre NR. Tissue hypoxia: implications for the respiratory clinician. Respir Care 2014;59(10):1590–6. doi:10.4187/respcare.03357.
[13] Hernandez G, Bruhn A, Luengo C, Regueira T, Kattan E, Fuentealba A, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. Intensive Care Med 2013;39(8):1435–43. doi:10.1007/s00134-013-2982-0.
[14] Vellinga NA, Boerma EC, Koopmans M, Donati A, Dubin A, Shapiro NI, et al. International study on microcirculatory shock occurrence in acutely ill patients. Crit Care Med 2015;43(1):48–56. doi:10.1097/CCM.0000000000000553.
[15] Alegría L, Vera M, Dreyse J, Castro R, Carpio D, Henriquez C, et al. A hypoperfusion context may aid to interpret hyperlactatemia in Sepsis-3 septic shock patients: a proof-of-concept study. Ann Intensive Care 2017;7(1):29. doi:10.1186/s13613-017-0253-x.
[16] Hernandez G, Bruhn A, Castro R, Regueira T. The holistic view on perfusion monitoring in septic shock. Curr Opin Crit Care 2012;18(3):280–6. doi:10.1097/MCC.0b013e3283532c08.
[17] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40(12):1795–815. doi:10.1007/s00134-014-3525-z.
[18] 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;315(8):801–10. doi:10.1001/jama.2016.0287.
[19] Hernandez G, Luengo C, Bruhn A, Kattan E, Friedman G, Ospina-Tascon GA, et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. Ann Intensive Care 2014;4:30. doi:10.1186/s13613-014-0030-z.
[20] Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med 2019;45(1):82–5. doi:10.1007/s00134-018-5213-x.
[21] 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. Crit Care Med 2017;45(3):486–552. doi:10.1097/CCM.0000000000002255.
[22] Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care 2015;19(Suppl 3):S8. doi:10.1186/cc14726.
[23] Morelli A, Passariello M. Hemodynamic coherence in sepsis. Best Pract Res Clin Anaesthesiol 2016;30(4):453–63. doi:10.1016/j.bpa.2016.10.009.
[24] Arnemann PH, Hessler M, Kampmeier T, Seidel L, Malek Y, Van Aken H, et al. Resuscitation with hydroxyethyl starch maintains hemodynamic coherence in ovine hemorrhagic shock. Anesthesiology 2020;132(1):131–9. doi:10.1097/ALN.0000000000002998.
[25] Hernández G, Castro R, Bakker J. Capillary refill time: the missing link between macrocirculation and microcirculation in septic shock. J Thorac Dis 2020;12(3):1127–9. doi:10.21037/jtd.2019.12.102.
[26] Messina A, Greco M, Cecconi M. What should I use next if clinical evaluation and echocardiographic haemodynamic assessment is not enough. Curr Opin Crit Care 2019;25(3):259–65. doi:10.1097/MCC.0000000000000603.
[27] Brunauer A, Koköfer A, Bataar O, Gradwohl-Matis I, Dankl D, Bakker J, et al. Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: a pilot study. J Crit Care 2016;35:105–9. doi:10.1016/j.jcrc.2016.05.007.
[28] Jacquet-Lagrèze M, Bouhamri N, Portran P, Schweizer R, Baudin F, Lilot M, et al. Capillary refill time variation induced by passive leg raising predicts capillary refill time response to volume expansion. Crit Care 2019;23(1):281. doi:10.1186/s13054-019-2560-0.
[29] Hariri G, Joffre J, Leblanc G, Bonsey M, Lavillegrand JR, Urbina T, et al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. Ann Intensive Care 2019;9(1):37. doi:10.1186/s13613-019-0511-1.
[30] Lima A, van Bommel J, Sikorska K, van Genderen M, Klijn E, Lesaffre E, et al. The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients. Crit Care Med 2011;39(7):1649–54. doi:10.1097/CCM.0b013e3182186675.
[31] Lima A, Jansen TC, van Bommel J, Ince C, Bakker J. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med 2009;37(3):934–8. doi:10.1097/CCM.0b013e31819869db.
[32] Jouffroy R, Saade A, Tourtier JP, Gueye P, Bloch-Laine E, Ecollan P, et al. Skin mottling score and capillary refill time to assess mortality of septic shock since pre-hospital setting. Am J Emerg Med 2019;37(4):664–71. doi:10.1016/j.ajem.2018.07.010.
[33] Hernández G, Teboul JL. Is the macrocirculation really dissociated from the microcirculation in septic shock. Intensive Care Med 2016;42(10):1621–4. doi:10.1007/s00134-016-4416-2.
[34] Hernández G, Cavalcanti AB, Ospina-Tascón G, Zampieri FG, Dubin A, Hurtado FJ, et al. Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK – a randomized controlled trial. Ann Intensive Care 2018;8(1):52. doi:10.1186/s13613-018-0398-2.
[35] Hernández G, Cavalcanti AB, Ospina-Tascón G, Dubin A, Hurtado FJ, Damiani LP, et al. Statistical analysis plan for early goal-directed therapy using a physiological

holistic view – the ANDROMEDA-SHOCK: a randomized controlled trial. Rev Bras Ter Intensiva 2018;30(3):253–63. doi:10.5935/0103-507X.20180041.

[36] Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A Bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med 2020;201(4):423–9. doi:10.1164/rccm.201905-0968OC.

[37] Castro R, Kattan E, Ferri G, Pairumani R, Valenzuela ED, Alegría L, et al. Effects of capillary refill time-vs. lactate-targeted fluid resuscitation on regional, microcirculatory and hypoxia-related perfusion parameters in septic shock: a randomized controlled trial. Ann Intensive Care 2020;10(1):150. doi:10.1186/s13613-020-00767-4.

[38] Lara B, Enberg L, Ortega M, Leon P, Kripper C, Aguilera P, et al. Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. PLoS ONE 2017;12(11):e0188548. doi:10.1371/journal.pone.0188548.

[39] Shinozaki M, Nakada TA, Kawaguchi R, Yoshimura Y, Nakaguchi T, Haneishi H, et al. Feedback function for capillary refilling time measurement device. Crit Care 2019;23(1):295. doi:10.1186/s13054-019-2570-y.

[40] Kawaguchi R, Nakada TA, Oshima T, Shinozaki M, Nakaguchi T, Haneishi H, et al. Optimal pressing strength and time for capillary refilling time. Crit Care 2019;23(1):4. doi:10.1186/s13054-018-2295-3.

[41] Marty P, Roquilly A, Vallée F, Luzi A, Ferré F, Fourcade O, et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 h in Intensive Care Unit: an observational study. Ann Intensive Care 2013;3(1):3. doi:10.1186/2110-5820-3-3.

[42] Bakker J, de Backer D, Hernandez G. Lactate-guided resuscitation saves lives: we are not sure. Intensive Care Med 2016;42(3):472–4. doi:10.1007/s00134-016-4220-z.

[43] Hernández G, Kattan E, Ospina-Tascón G, Bakker J, Castro RANDROMEDA-SHOCK Study Investigators and the Latin America Intensive Care Network (LIVEN). Capillary refill time status could identify different clinical phenotypes among septic shock patients fulfilling Sepsis-3 criteria: a post hoc analysis of ANDROMEDA-SHOCK trial. Intensive Care Med 2020;46(4):816–18. doi:10.1007/s00134-020-05960-4.

[44] Marik PE. Lactate guided resuscitation-nothing is more dangerous than conscientious foolishness. J Thorac Dis 2019;11(Suppl 15):S1969–72. doi:10.21037/jtd.2019.07.67.

[45] Spiegel R, Gordon D, Marik PE. The origins of the Lacto-Bolo reflex: the mythology of lactate in sepsis. J Thorac Dis 2020;12(Suppl 1):S48–53. doi:10.21037/jtd.2019.11.48.

[46] Kattan E, Hernández G, Ospina-Tascón G, Valenzuela ED, Bakker J, Castro R, et al. A lactate-targeted resuscitation strategy may be associated with higher mortality in patients with septic shock and normal capillary refill time: a post hoc analysis of the ANDROMEDA-SHOCK study. Ann Intensive Care 2020;10(1):114. doi:10.1186/s13613-020-00732-1.