Macrocirculation and Microcirculation: The "Batman and Superman" Story of Critical Care Resuscitation

Ashish K. Khanna, MD, FCCP, FCCM,*† and Kunal Karamchandani, MD, FCCP‡

GLOSSARY

CI = cardiac index; **CRT** = capillary refill time; **ICU** = intensive care unit; **MAP** = mean arterial pressure; **MFI** = microvascular flow index; **OPS** = orthogonal polarization spectrum; **PPV** = proportion of perfused vessels; **RBC** = red blood cells; **SDF** = sidestream dark field

The goal of circulatory resuscitation in critically ill patients is to restore adequate oxygen delivery, tissue perfusion, and ultimately cellular metabolism. The circulatory system is tasked with providing adequate blood flow to deliver oxygen and other nutrients and removing end products of metabolism at the tissue level. To do so, it has to generate adequate perfusion pressure to drive blood into the capillaries. It remains frustratingly unclear whether the assessment of circulatory adequacy should focus on pressure, flow, or both and in what priority order. While a predefined mean arterial pressure (MAP) is recommended by international guidelines[1] and is the most common approach, recent evidence suggests that MAP may not correlate with adequacy of blood flow through end-capillaries (microcirculation), and that microcirculatory dysfunction can persist despite normal MAP.[2,3]

One explanation for this lack of correlation between MAP and microcirculation is that the 2 circulations are not coupled during states of critical illness. This loss of hemodynamic coherence between the macro- and microcirculatory function creates a conundrum for the practicing intensivist who must manage hemodynamics at the systemic level as well as at the level of end-capillaries. In such a scenario, clinicians must not only decide whether to prioritize the macro- or microcirculation initially but also identify clear metrics for transitioning between optimizing these 2 at different times of critical illness.

The microcirculation, composed of arterioles, capillaries, and venules, is the circulatory element in direct contact with parenchymal cells. Under physiological conditions, the microcirculation represents about 10% of the circulating blood volume and plays a vital role in oxygen delivery and waste removal from tissues. To fulfill this role, it needs to direct adequate blood flow to tissue regions with higher metabolic demands. However, during septic shock, microcirculatory changes due to endothelial dysfunction, glycocalyx degradation, altered blood cell rheology (reduced red blood cells [RBC] deformability), and imbalance between the levels of vasodilating and vasoconstricting substances may all alter the matching of blood flow to tissue demand. Clearly the microcirculation acts as a tissue perfusion "gate keeper" and should be prioritized during resuscitation. However, optimizing microvascular perfusion is complicated by the need to perfuse just some of the beds, some of the time—with no good way to identify which ones these are, and no tools that let us do this selectively by organ system.

Although specialized imaging can evaluate microcirculatory performance and metrics such as proportion of perfused vessels (PPV) and microvascular flow index (MFI) have been proposed, this technology is not universally available. Recent studies evaluating automated quantification of microcirculatory variables as well as incorporating real-time techniques as part of intensive care unit (ICU) nurse routine surveillance are steps in the right direction.[4,5] A limitation of microcirculatory imaging is that it explores only 1 site, most commonly sublingual tissue, which

From the *Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest School of Medicine, Wake Forest Baptist Health Network, Winston-Salem, North Carolina; †Outcomes Research Consortium, Cleveland, Ohio; and ‡Department of Anesthesiology & Perioperative Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania.

Accepted for publication September 30, 2020.

Funding: A. K. Khanna has funding from a Wake Forest Clinical and Translational Science Institute (CTSI) NIH/NCTAS KL2 TR001421 award for a trial on continuous postoperative hemodynamic and saturation monitoring.

Conflicts of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Kunal Karamchandani, MD, FCCP, Department of Anesthesiology & Perioperative Medicine, H187, Penn State Health Milton S. Hershey Medical Center, 500 University Dr, Hershey, PA 17033. Address e-mail to kkaramchandani@pennstatehealth.psu.edu.

DOI: 10.1213/ANE.0000000000005272

may not respond to fluid in the same way as other microvascular territories.[6] Furthermore, both saliva between the probe and the mucosa and application of excessive pressure by the probe can impair the accuracy of the readings.[7] A potential alternative to monitoring the microcirculation via sublingual imaging is to assess capillary refill time (CRT). The CRT measures the amount of time necessary for the skin to return to baseline color after applying a pressure on a soft tissue (most commonly the fingertip).[8] Although CRT measurement may also be challenging,[9] recent evidence suggests that monitoring the peripheral perfusion using CRT is equivalent to monitoring global oxygen delivery using lactate measurement.[10]

In addition to challenges in measurement, how best to treat microcirculatory abnormalities is also unclear.[11] Almost all treatment modalities that address microcirculatory changes also affect the microcirculation. An example is the use of nitrates to improve the microcirculatory dysfunction associated with sepsis. Although they may improve microcirculatory flow, they also exert a hypotensive effect that may mitigate their microcirculatory effect.[12] The arrival of a microcirculation-specific therapy with no or minimal effect on the macrocirculation may address this issue.

In such a situation, blood pressure–guided resuscitation that targets the macrocirculation may be a reasonable starting point. The use of blood pressure to assess tissue perfusion in critically ill patients has the largest experience and evidence base, associations between hypotension and poor outcomes are robust in the critical care environment, and potential adverse consequences of vasoactive medications are well known.[13] A logical next step would be to monitor for adverse consequences of macrocirculatory resuscitation on the microcirculation because strategies to address blood pressure and cardiac output may not improve microcirculatory function. Volume expansion, for example, may affect blood pressure and cardiac index without affecting microvascular perfusion.[14,15] Use of vasoactive agents such as norepinephrine may increase MAP and improve microcirculation in septic patients with an abnormal baseline microcirculation, but this increase can be detrimental in patients with previously normal microcirculation.[16]

In addition to an uncertain relationship between blood pressure optimization and microcirculatory adequacy, optimal macrocirculatory targets for resuscitation are also unclear. Based on trials finding fewer cardiac arrhythmias, less vasopressor use, and similar mortality at higher and lower MAP targets, the 2016 Surviving Sepsis guidelines recommend targeting a minimum MAP of 65 mm Hg.[1] However, large retrospective cohort studies find that the risk of myocardial injury, acute kidney injury, and mortality may increase at much higher threshold pressures.[13] A similar association between hypotension and major adverse cardiovascular and cerebrovascular events has been reported intraoperatively.[17] While prospective randomized tests of higher MAP for end organ preservation have not validated a causal relationship,[18,19] they leave open the possibility that, if patients do not improve at standard MAPs then targeting higher MAPs may be effective.[17] In reality, it may be prudent to adjust the macrocirculatory variables such as MAP to meet perfusion requirements, without designating an absolute value as normal or as a target of resuscitative efforts.

So, what should the 2020 clinician do to assess and manage the adequacy of hemodynamic resuscitation? Although few data exist to guide the integrated use of both macro- and microcirculatory targets, a pragmatic approach might be to first address the macrocirculatory targets. This is especially relevant in the early stages of septic shock, when the microcirculation is still functionally preserved and early resuscitation with maneuvers that restore the macrocirculatory variables (cardiac output, MAP, etc) may improve microcirculatory flow.[20] If the patient improves clinically, no microcirculatory monitoring or intervention is likely needed. However, if the patient does not improve, or if end organ function deteriorates, it probably indicates loss of hemodynamic coherence. In such situations, interventions targeting the macrocirculation may be detrimental to the microcirculation. Hence, at this point, monitoring of the microcirculation and instituting interventions targeted at microcirculatory resuscitation are reasonable. Considering the lack of robust clinical data around microcirculation-guided resuscitation, such interventions should only be continued if they are not adversely impacting the macrocirculatory variables. The Figure depicts an algorithm suggesting a macrocirculation- and microcirculation-based resuscitation strategy in patients with septic shock. An early identification of loss of hemodynamic coherence is important, and the emerging role of CRT as a readily available, bedside tool that could reliably detect such dissociation between the macro- and microcirculation needs further exploration.

The debate on targeting the macro- or microcirculation to guide resuscitation has persisted for the last 2 decades without resolution. Two challenges defy resolution. The first is the lack of coherence between macro- and microcirculatory performance. That patients may have adequate macrocirculatory function with inadequate microcirculatory function (or vice versa), and that both macro- and microcirculatory performance may affect outcome suggests that both circulations need addressing during resuscitation. The second challenge is that specific therapies targeting either the macro- or microcirculation may actually affect each other adversely. In this way, the

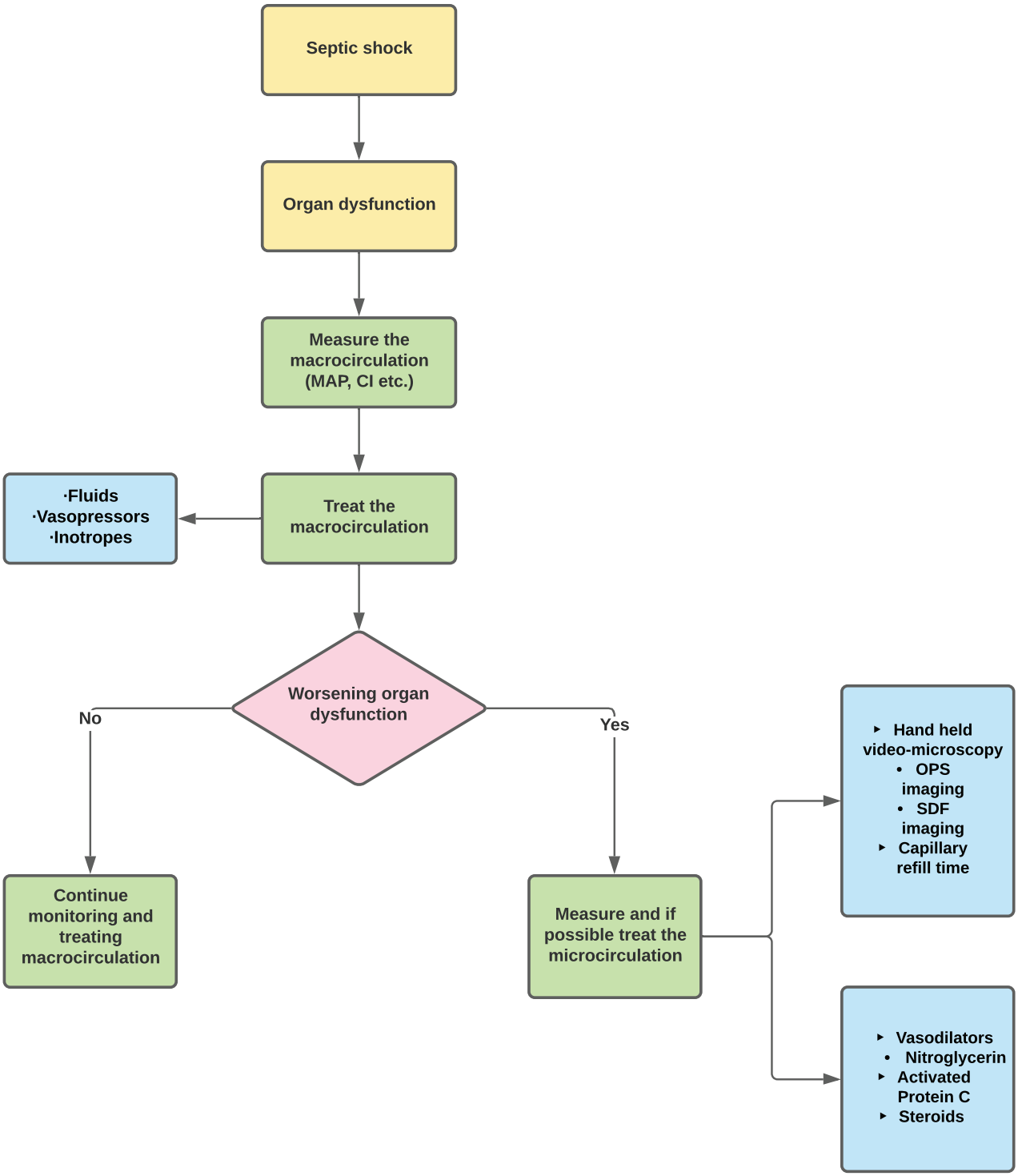

Figure. Macrocirculation- and microcirculation-based resuscitation strategy in patients with septic shock. CI indicates cardiac index; MAP, mean arterial pressure; OPS, orthogonal polarization spectrum; SDF, sidestream dark field.

macro- and microcirculations may be like "Batman" and "Superman." Both fight the crime of sepsis-induced hemodynamic instability, but differ in their approach and methods. Clearly, Batman and Superman are both superheroes in their own right, and share a vital relationship without which we would not know the world as we know it today!

DISCLOSURES

Name: Ashish K. Khanna, MD, FCCP, FCCM.
Contribution: This author helped write and edit the manuscript.
Conflicts of Interest: A. K. Khanna consults for Edwards Lifesciences, Retia Medical and Zoll Medical.
Name: Kunal Karamchandani, MD, FCCP.
Contribution: This author helped write and edit the manuscript.

Conflicts of Interest: None.
This manuscript was handled by: Avery Tung, MD, FCCM.

REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304–377.
2. Dünser MW, Takala J, Brunauer A, Bakker J. Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. *Crit Care*. 2013;17:326.
3. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004;32:1825–1831.
4. Hilty MP, Guerci P, Ince Y, Toraman F, Ince C. MicroTools enables automated quantification of capillary density and red blood cell velocity in handheld vital microscopy. *Commun Biol*. 2019;2:217.
5. Tanaka S, Harrois A, Nicolaï C, et al. Qualitative real-time analysis by nurses of sublingual microcirculation in intensive care unit: the MICRONURSE study. *Crit Care*. 2015;19:388.
6. Edul VS, Ince C, Navarro N, et al. Dissociation between sublingual and gut microcirculation in the response to a fluid challenge in postoperative patients with abdominal sepsis. *Ann Intensive Care*. 2014;4:39.
7. Ince C, Boerma EC, Cecconi M, et al; Cardiovascular Dynamics Section of the ESICM. Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2018;44:281–299.
8. Hernandez G, Luengo C, Bruhn A, et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. *Ann Intensive Care*. 2014;4:30.
9. Alsma J, van Saase JLCM, Nanayakkara PWB, et al; FAMOUS Study Group*. The power of flash mob research: conducting a nationwide observational clinical study on capillary refill time in a single day. *Chest*. 2017;151:1106–1113.
10. Hernández G, Ospina-Tascón GA, Damiani LP, et al; The ANDROMEDA SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). 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;321:654–664.
11. Monnet X, Saugel B. Could resuscitation be based on microcirculation data? We are not sure. *Intensive Care Med*. 2018;44:950–953.
12. Lima A, van Genderen ME, van Bommel J, Klijn E, Jansem T, Bakker J. Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock. *Crit Care*. 2014;18:R126.
13. Khanna AK, Maheshwari K, Mao G, et al. Association between mean arterial pressure and acute kidney injury and a composite of myocardial injury and mortality in postoperative critically ill patients: a retrospective cohort analysis. *Crit Care Med*. 2019;47:910–917.
14. Monge García MI, Guijo González P, Gracia Romero M, et al. Effects of fluid administration on arterial load in septic shock patients. *Intensive Care Med*. 2015;41:1247–1255.
15. Ospina-Tascon G, Neves AP, Occhipinti G, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med*. 2010;36:949–955.
16. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care*. 2009;13:R92.
17. Smischney N, Shaw A, Stapelfeldt W, et al. 390: postoperative hypotension in the critically ill is associated with adverse clinical outcomes. *Crit Care Med*. 2020;48:177.
18. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370:1583–1593.
19. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. *JAMA*. 2020;323:938–949.
20. Kattan E, Castro R, Vera M, Hernández G. Optimal target in septic shock resuscitation. *Ann Transl Med*. 2020;8:789.