Elisa *et al. Critical Care* (2026) 30:354
https://doi.org/10.1186/s13054-026-06187-3

Critical Care

MATTERS ARISING Open Access

Beyond shear stress: septic microvascular failure remains a multifactorial phenomenon

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Dear Editor,

We read with great interest the article by Popovich recently published in Critical Care [1]. Popovich proposes an elegant conceptual model in which microvascular failure in septic shock becomes the predictable consequence of three interacting variables: global vasodilation, limited cardiac output and shear-stress regulation [1]. The key mathematical point is sound: if shear stress is to be maintained to avoid capillary derecruitment, the flow required by any individual vessel will rise with the cube of its radius. It follows that global arteriolar dilation will impose a flow demand that even a hyperdynamic circulation cannot meet. This model is attractive because it offers a simple and straightforward explanation for the hemodynamic incoherence described in septic shock [2]. However, the danger lies in crossing the line between simple and simplistic: a mathematical model showing that one mechanism can reproduce a phenotype does not establish that the mechanism is dominant, necessary, or clinically relevant in vivo.

The proposed framework simplifies the structure of the vascular network to a degree that limits biological interpretation. The septic microcirculation is unlikely to be a set of independent parallel arterioles with a common shear target. It is a hierarchical, branching, heterogeneous network in which vessel diameter, pressure, hematocrit distribution, local metabolism, endothelial signaling, leukocyte adhesion, coagulation and red blood cell rheology interact. Endothelial mechanotransduction is undeniably altered in sepsis, due to a derangement of the glycocalyx [3]. However, the endothelial glycocalyx also participates in coagulation and inflammatory signaling, and exerts a crucial barrier function [3]. Alteration of the glycocalyx enhances leukocyte-endothelium interactions, exposes a pro-coagulant surface triggering the formation of microthrombi, and increases microvascular permeability leading to tissue oedema [3]. By using sublingual videomicroscopy and calculating the perfused boundary region as an index of glycocalyx dysfunction, we showed that septic patients exhibit altered glycocalyx, which correlates with the number of rolling leukocytes visible in the venular microvessels [4]. In a recent study by our group, sepsis-induced coagulopathy was associated with microvascular rarefaction over the first 4 days of sepsis and glycocalyx shedding was associated with more severe worsening in vessel density parameters [5]. Although of crucial importance, altered shear sensing is only one of the several complex aspects that characterize sepsis-induced microvascular dysfunction. Moreover, the "apparent shear target" introduced by Popovich [1] is another vulnerable point of the model: as it is not currently a measurable clinical or experimental variable and cannot be independently quantified, it risks becoming a free parameter that makes the model fit the expected direction of change without testing the underlying biology. The existence of altered mechanosensing does not by itself prove that the endothelium behaves as if it were pursuing an increased shear target.

The therapeutic implications should therefore be interpreted cautiously. Based on his model, Popovich suggests that vasoactive therapies that reduce global vasodilation or lower the apparent shear target should restore

This comment refers to the article available online at https://doi.org/10.1186/s13054-026-06156-w.

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microvascular coherence without requiring supranormal cardiac output [1]. Nonetheless, current human data do not support a uniform microcirculatory response to vasoactive agents [6]. The endothelium in sepsis is generally hyporesponsive to catecholamines due to cytokine storm and enhanced nitric oxide production. The response of the microcirculation to vasoconstrictors is highly heterogeneous: increasing norepinephrine doses failed to yield a consistent improvement in microvascular blood flow in septic shock patients [7]. On the other hand, the use of inotropes such as dobutamine to increase the cardiac output did not result in a consistent improvement in microvascular blood flow [8]. Such findings are more compatible with patient-specific, context-dependent microvascular behavior rather than with a single network constraint.

The shear stress model is valuable as a hypothesis-generating construct. Such hypothesis should be tested against quantitative microcirculatory datasets and responses to vasoactive interventions.

In conclusion, Popovich proposed a stimulating and physiologically sound model, but septic microvascular failure remains a multifactorial and highly-complex phenomenon. The appropriate conclusion is not that microvascular failure is inevitable, but that shear stress may be one potentially important constraint within a much larger and experimentally unresolved system.

Acknowledgements
None.

Author contributions
All authors conceived the content of the manuscript. ED and AD wrote the manuscript. All authors revised the manuscript and approved its final version.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 30 June 2026 / Accepted: 1 July 2026
Published online: 06 July 2026

References

1. Popovich I. On the inevitability of microvascular failure in septic shock and other vasodilatory conditions. Crit Care. 2026. https://doi.org/10.1186/s13054-026-06156-w.
2. Bakker J, Ince C. Monitoring coherence between the macro and microcirculation in septic shock. Curr Opin Crit Care. 2020;26:267–72.
3. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. Crit Care. 2019;23:16.
4. Donati A, Damiani E, Domizi R, Romano R, Adrario E, Pelaia P, et al. Alteration of the sublingual microvascular glycocalyx in critically ill patients. Microv Res. 2013;90:86–9.
5. Damiani E, Domizi R, Carsetti A, Antolini R, Scorcella C, Casarotta E, et al. The interplay between microcirculatory dysfunction and coagulopathy in patients with sepsis: an exploratory single-center observational study. J Crit Care. 2026;95:155663.
6. Potter EK, Hodgson L, Creagh-Brown B, Forni LG. Manipulating the microcirculation in sepsis – the impact of vasoactive medications on microcirculatory blood flow: a systematic review. Shock. 2019;52:5–12.
7. Dubin A, Pozo MO, Casabella CA, Palizas F Jr, Murias G, Museinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care. 2009;13:R92.
8. 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;39:1435–43.

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