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Review Article

VASODILATORS IN SEPTIC SHOCK RESUSCITATION: A CLINICAL PERSPECTIVE

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ABSTRACT—Microcirculatory abnormalities have been shown to be frequent in patients with septic shock despite "normalization" of systemic hemodynamics. Several studies have explored the impact of vasodilator therapy (prostacyclin, inhaled nitric oxide, topic acetylcholine, and nitroglycerin) on microcirculation and tissue perfusion, with contradictory findings. In this narrative review, we briefly present the pathophysiological aspects of microcirculatory dysfunction, and depict the evidence supporting the use of vasodilators and other therapeutic interventions (fluid administration, blood transfusion, vasopressors, and dobutamine) aiming to improve the microcirculatory flow in septic shock patients.

KEYWORDS—Microcirculation, multiple organ failure, nitric oxide, nitroglycerin, resuscitation, sepsis, septic shock, vasodilator agents

INTRODUCTION

Microcirculation is composed of small vessels such as arterioles, capillaries, and venules, with a diameter lower than 100 μm (1). In fact, the small vessels (diameter ≤20–25 μm), i.e., capillaries and post-capillary venules, represent the primary site of oxygen exchange between red blood cells (RBC) and tissue cells (1). Microcirculatory blood flow is markedly disturbed in sepsis (2–4) with a clear association between persistent microcirculatory abnormalities, increased morbidity, and poor outcomes (5). Therefore, it has been postulated that interventions aiming to recruit microcirculation, i.e., open non-perfused or intermittently perfused capillaries might improve tissue perfusion, mitigating the progression to organ failure and death (6).

According to Poiseuille's law, blood flow through the capillaries is proportional to the pressure gradient between post-arteriolar and venular pressures (microcirculatory driving pressure) and the fourth power of the radius, and inversely proportional to capillary length and blood viscosity (Fig. 1). Therefore, while the systemic perfusion pressure is determined by the difference between mean arterial blood pressure (MAP) and central venous pressure, the perfusion pressure in the microcirculation (microcirculatory driving pressure) is the net result of precapillary inflow pressure (approximately 30 mm Hg) minus venular outflow pressure (approximately 10 mm Hg) (Fig. 2) (7–9).

Theoretically, the administration of vasodilating agents, such as acetylcholine (2), nitric oxide (NO) donors (10), and nitroglycerin (11), might improve microcirculatory blood flow by increasing the precapillary inflow pressure while the venular outflow pressure is maintained, i.e., by increasing the microcirculatory driving pressure (Fig. 2) (8, 9).

The use of vasodilators as adjuvant therapy in the treatment of circulatory shock was introduced into clinical practice in the 1960s (12–14). Nevertheless, the concept supporting vasodilators use to optimize microcirculatory perfusion in critical ill patients was only tested in the 1990s. These studies suggested that different vasodilators, such as prostacyclin (15) and inhaled NO (16), might improve splanchnic perfusion. In the past years, several studies have explored the impact vasodilators (prostacyclin, inhaled nitric oxide, topic acetylcholine, and nitroglycerin) on microcirculation and tissue perfusion with contradicting findings.

In this narrative review, we briefly present the pathophysiology of microcirculatory dysfunction, and depict the evidence supporting the use of vasodilators and other therapeutic interventions (fluid administration, blood transfusion, vasopressors, and dobutamine) aiming to improve the microcirculatory flow in septic shock patients.

MECHANISMS PROMOTING MICROVASCULAR DYSFUNCTION

Blood flow through the capillary network is tightly controlled by the arteriolar resistance vessels—the arteriolar network (17, 18). Arterioles are surrounded by a smooth muscle layer, which can contract or relax in response to tissue oxygen tension and the presence of vasoactive agents, such as acetylcholine, catecholamines, prostaglandins, endothelin, bradykinin, thromboxane, and NO (19). Microcirculation perfusion is regulated by an intricate interplay of neuroendocrine,

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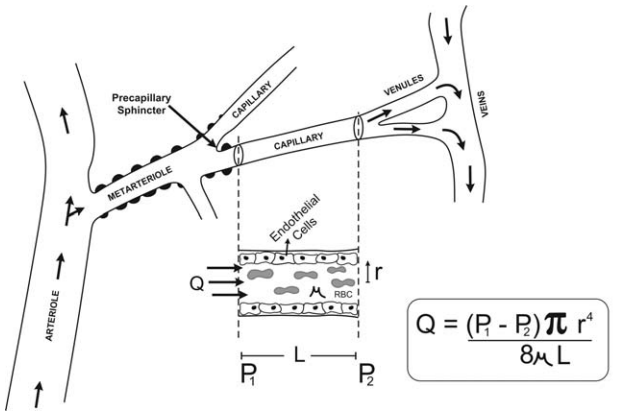

Fig. 1. **The main determinants of the microcirculatory blood flow accordingly to the Poiseuille's law.** Blood flow through the capillaries (Q) is proportional to the pressure gradient between post-arteriolar (P1) and venular pressures (P2), i.e., the microcirculatory driving pressure (P1-P2), and by the fourth power of the capillary radius (r4), and is inversely proportional to capillary length (L) and blood viscosity (μ). The black arrows represent the blood flow direction through microvessels. RBC indicates red blood cells.

paracrine, and mechanosensory pathways (20). These mechanisms control oxygen delivery to the tissues according to the cellular metabolic demand (17, 21). Under physiological conditions, NO acts as endogenous vasodilator and the endothelium regulates blood flow to the tissues by "recruiting microvessels" through NO release (22). In sepsis, the NO system becomes severely disturbed due to a heterogeneous expression of the inducible nitric oxide synthase (23). Moreover, NO can also be consumed by reactive oxygen species, producing localized areas of relative NO deficiency in the microvascular bed (24). This might explain, at least in part, the pathologic heterogeneity of microvascular blood flow observed in both experimental (25) and human sepsis (3).

The relationship between circulating cells and endothelial surface cells is crucial in sepsis pathophysiology (26). Glycocalyx is a thin layer of glycosaminoglycan that covers the endothelial surface and has the function of facilitating RBC, white blood cells, and platelets flow through the capillaries (27). During sepsis, glycocalyx layer thickness is reduced (27), thus increasing leukocytes and platelets adhesion to the endothelial cells, and promoting endothelial dysfunction (28). Finally, decreased RBC rheology (29, 30), increased blood viscosity (31), increased number of activated neutrophils (32), activation of coagulation, and complement systems with fibrin deposition in the microvascular bed (33), along with derangements of vascular autoregulatory mechanisms (34), represent mechanisms that further compromise microcirculation and oxygen delivery in septic shock.

MICROCIRCULATION IN SEPTIC SHOCK

De Backer et al. (2) published the first study addressing the sublingual microcirculation in septic shock patients with orthogonal polarization spectral imaging (OPS) in 2002 . Their findings were confirmed by several other authors (4, 35), demonstrating that microcirculatory abnormalities in septic shock are more pronounced in small vessels, i.e., capillaries (2), and do not improve over time in non-survivors (5).

Microcirculatory abnormalities in septic shock are characterized by a decrease in total vessel density and perfused capillary density—a surrogate of functional capillary density, as well as a decrease in proportion of perfused capillaries (PPV) (2). At the same time, the proportion of non-perfused and intermittently perfused capillaries increased (2), along with the flow heterogeneity within areas in the same organ separated by few millimeters (3, 11, 36). Furthermore, capillaries that do not exhibit blood flow at a given time can become perfused few seconds or minutes later, demonstrating the dynamic behavior of microcirculation under septic conditions (6).

Additionally, it was demonstrated in 26 severe sepsis and septic shock patients during the first 6 h of resuscitation that microvascular blood flow (microvascular flow index [MFI]) was slower and more heterogeneous (flow heterogeneity index [FHI]) in non-survivals compared with survivals (3). These data are in agreement with findings reported by Trzeciak et al., who demonstrated that septic shock patients who improved their sequential organ failure assessment (SOFA) score during the first 24 h of resuscitation exhibited a higher improvement in microvascular blood flow (MFI) compared with patients who did not improve their SOFA score (37). Finally, it was demonstrated that PPV was independently associated with intensive care unit (ICU) survival in severe sepsis and septic shock patients (4).

These observations led to a growing interest in monitoring microcirculation as a valuable adjunct to standard global parameters to predict or diagnose ongoing tissue hypoperfusion (1). Indeed, many studies, particularly on sepsis, have highlighted the importance of clinical evaluation of microcirculation as part of tissue perfusion monitoring in shock (6). As a result, many authors have advocated that therapeutic interventions aiming to improve microcirculation would boost tissue perfusion and, consequently, mitigate the progression toward organ failure and death in septic shock patients (6, 21).

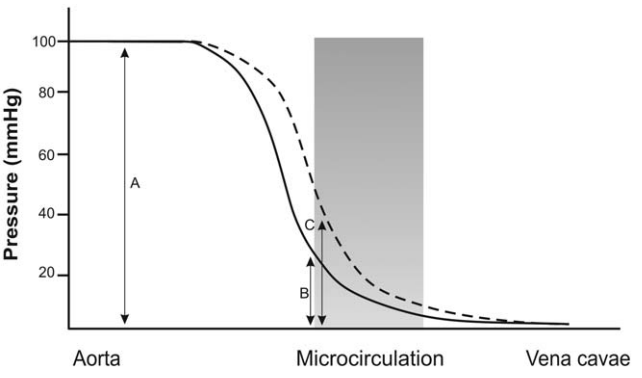

Fig. 2. **The effect of vasodilators on the microcirculatory driving pressure and on the microcirculatory blood flow.** A: systemic perfusion pressure (difference between mean arterial blood pressure and central venous pressure), B: microcirculatory driving pressure (precapillary inflow pressure minus venular outflow pressure), and C: theoretical effect of a vasodilating administration improving microcirculatory blood flow by increasing the precapillary inflow pressure while the venular outflow pressure is maintained (increased microcirculatory driving pressure). Modified from (23) with permission.

VASODILATORS AND THEIR EFFECTS IN MICROCIRCULATION

The concept of using pharmacotherapy to optimize the microcirculatory blood flow in critically ill patients gained notoriety in the late 1980s, when clinical trials addressing the effects of drugs with vasodilation properties such as prostacyclin (38) and dobutamine were published (39). Afterward, several studies have explored the impact of vasodilating agents such as prostacyclin, inhaled NO, topic acetylcholine and nitroglycerin in microcirculation, tissue perfusion, organ function, and mortality (Table 1).

The effect of vasodilator therapy in clinical sepsis was first demonstrated with the use of topical nitroglycerin in postoperative patients complicated by severe sepsis resulting in improvement in cardiac output (CO) and oxygen consumption (40). More recently, it has been demonstrated that administration of vasodilating agents, such as acetylcholine (2) or NO donors (10), was effective in recruiting capillaries of sublingual microcirculation in clinical and experimental sepsis. These observations had important implications, indicating that microvascular derangements could be reversed with drugs (2). Therefore, strategies aiming to open microcirculation through systemic vasodilators became a target for new studies (6) (Table 1).

Pittet et al. (41) demonstrated in a small crossover study that by increasing systemic oxygen delivery (DO_2) through a 30-min intravenous infusion of prostacyclin, there was an increase in systemic oxygen consumption (VO_2) and skin microvascular blood flow. In another small non-controlled study, continuous intravenously prostacyclin infusion up to 32 days enhanced gastric mucosal pH (pHi), suggesting an improved splanchnic blood flow (15). Similar findings were demonstrated by Eichelbrönner et al. (16), who reported that aerosolized prostacyclin was effective to increase pHi and reduce arterial-gastric mucosal pressure of carbon dioxide difference (PCO_2 gap), while hepatic blood flow, systemic hemodynamics, DO_2 and VO_2 were not affected.

After the development of OPS imaging, it was demonstrated that topic acetylcholine applied to the sublingual region improved microvascular blood flow in septic shock patients (2, 42). By proving the ''recruitable'' aspect of microcirculation, Spronk et al. (11) demonstrated in a prospective open label trial that intravenously nitroglycerin (0.5 mg loading dose followed by a continuous infusion of 0.5– 4.0 mg/h) improved microvascular flow in fluid resuscitated septic shock patients.

Following this initial report, Boerma et al. (43) randomized 70 fluid resuscitated severe sepsis and septic shock patients to receive either intravenously nitroglycerin (2 mg bolus in 30 min followed by 2 mg/h up to 24 h) or placebo (0.9% saline). The authors reported a similar improvement in sublingual capillary blood flow during the study period (up to 24 h) in both groups (43). An interesting finding presented in this trial was the lower number of organ dysfunctions in patients who received nitroglycerin compared with the placebo group (43).

More recently, Lima et al. (44) demonstrated that a stepwise increase in nitroglycerin infusion (starting from 2 mg/h up to 16 mg/h) improved peripheral perfusion in circulatory shock patients who persisted with abnormal peripheral perfusion after 6 h of resuscitation despite achieving macrohemodynamic stabilization. Finally, Trzeciak et al. (45) randomized 49 septic shock patients to receive either inhaled NO (40 ppm) or sham inhaled NO (placebo) for 6 h starting after the achievement of conventional macrohemodynamic goals (MAP $\geq$65 mm Hg, central venous oxygen saturation [$ScvO_2$] $\geq$70% or lactate clearance $\geq$10%). The authors reported no differences between the groups regarding microcirculatory flow or in-hospital mortality (45).

OTHER THERAPIES THAT MAY IMPROVE MICROCIRCULATION IN SEPTIC SHOCK

Fluid therapy

The main determinants of oxygen transport to the tissue cells are convection (convective transport of oxygen carrying RBC through capillaries) and diffusion (diffusion of oxygen from RBC to tissue cells mitochondria) (Fig. 3) (46). Convective flow is determined by the product of the rate at which RBC enter the capillaries (RBC/s), the RBC oxygen saturation (HbSat) and the oxygen-carrying capacity of a RBC at 100% of saturation (0.0362 pl O_2/RBC) (46). Oxygen diffusion from the capillary RBC to the tissue cells mitochondria is determined by Fick's law of diffusion. Accordingly, oxygen diffusion is the product of the oxygen gradient from RBC to mitochondria (pO_2Grad) and the diffusion coefficient (D) times the exchange surface (S) divided by the diffusion distance (d) from the RBC to the mitochondria (46).

Therefore, fluid administration can improve microcirculatory blood flow by improving the convective transport of oxygen (46). Furthermore, blood flow through capillaries is proportional to the driving pressure across the capillary and by the fourth power of the radius, and inversely proportional to capillary length and blood viscosity. Thus, volume expansion may also improve microvascular blood flow by increasing the driving pressure in microcirculation, decreasing blood viscosity, as well as decreasing the release of endogenous vasoconstrictors (increasing vessels radius) (6).

On the other hand, fluid overload may affect microcirculation by increasing venular outflow pressure (boost venous return) and, therefore, by decreasing microcirculatory driving pressure (convection) and/or by increasing diffusion distance (diffusion) between capillary RBC and tissue mitochondria (Fig. 3) (47).

Two observational studies demonstrated that timely fluid administration could improve microvascular perfusion (48, 49). Ospina-Tascon et al. (48) investigated 60 hypovolemic severe sepsis patients requiring volume expansion within 24 h (early) or after 48 h (late) of sepsis recognition. The authors demonstrated that volume expansion with Ringer Lactate or 4% albumin improved capillary blood flow only in early sepsis, whereas late fluid administration failed to improve microcirculation despite having increased CO and MAP (48). Fluid administration did not affect flow heterogeneity in either early or late sepsis (48).

Moreover, it was demonstrated that both passive leg raising and volume expansion with 500 mL of 0.9% saline or 6%

Table 1. **Studies addressing the efficacy and safety of vasodilating agents in septic patients**

First author, year	N	Vasodilator	Site	Device	Main study findings	Type of study
Pittet J-F, 1990 (41)	11	i.v. prostacyclin vs. i.v. phentolamine	Skin (inner thigh)	Laser Doppler flowmeter	Higher improvement in skin microvascular blood flow with prostacyclin infusion than with phentolamine	Prospective, interventional, randomized
Radermacher P, 1995 (15)	16	i.v. prostacyclin	Splanchnic (Gastric)	Gastric Tonometry	Prostacyclin infusion increased pHi with concomitant increase in DO_2. Oxygen consumption remained unchanged	Prospective, interventional, non-controlled
Eichelbrönner O, 1996 (16)	16	Aerosolized prostacyclin vs. inhaled NO	Splanchnic (Gastric)	Splanchnic (Gastric)	Only aerosolized prostacyclin increased pHi and reduced PCO_2 gap. Hepatic blood flow (Indocyanine-green plasma disappearance rate) remained unchanged	Prospective, interventional, randomized
De Backer D, 2002 (2)	11	Topic acetylcholine	Sublingual microcirculation	OPS imaging	Increased TVD and PPV (capillaries)	Prospective, interventional, non-randomized, non-controlled
De Backer D, 2006 (42)	10	Topic acetylcholine + dobutamine (5 mcg/kg/min)	Sublingual microcirculation	OPS imaging	Increased TVD, PPV and PVD (capillaries)	Prospective, interventional, non-randomized, non-controlled
Spronk PE, 2002 (11)	8	i.v. nitroglycerin	Sublingual microcirculation	OPS imaging	Improved capillary MFI	Prospective, interventional, non-controlled, open-label
Boerma EC, 2010 (43)	70	i.v. nitroglycerin vs. placebo	Sublingual microcirculation	SDF imaging	No differences after 24 hours of nitroglycerin or placebo regarding (small vessels) MFI, TVD, PPV, PVD and FHI	Prospective, placebo controlled, double-bind study
Lima A, 2014 (44)	15*	i.v. nitroglycerin	Skin	Pulse oximeter, NIRS	Increased CRT, PPI, StO_2 and ReO_2 while Tskin-diff decreased.	Prospective, interventional, non-controlled study
Trzeciak S, 2014 (45)	49	Inhaled NO vs. placebo	Sublingual microcirculation	SDF imaging	No differences after 2 hours of Inhaled NO or placebo on MFI and FHI	Prospective, placebo controlled, double-bind study

*Twelve of 15 patients included had septic shock.

CRT indicates capillary refill time; FHI, flow heterogeneity index; MFI, microvascular flow index; NIRS, near-infrared spectroscopy; OPS, orthogonal polarization spectral; PCO_2 gap, arterial-gastric mucosal pressure of carbon dioxide gap difference; pHi, gastric mucosal pH; PPI, peripheral perfusion index; PPV, proportion of perfused vessels; PVD, perfused vessel density; ReO_2, peripheral tissue reoxygenation rate after arterial occlusion test; SDF, sidestream dark field imaging; StO_2, tissue oxygen saturation; Tskin-diff, forearm-to-fingertip skin temperature difference; TVD, total vessel density.

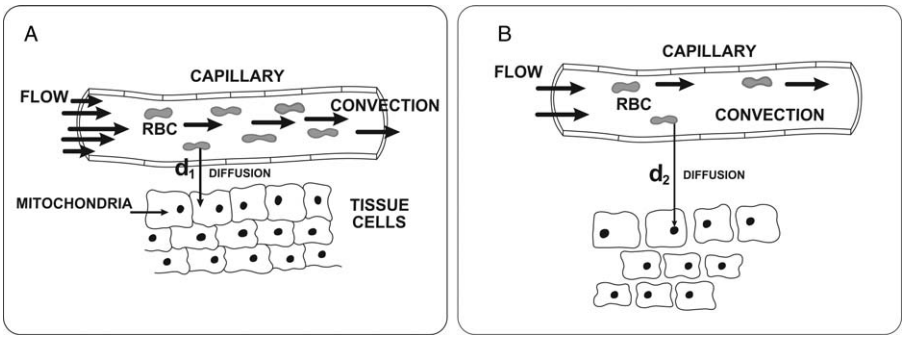

FIG. 3. **The effects of fluid overload on microcirculatory blood flow.** Convective flow is determined by the product of the rate at which red blood cells (RBC) enter the capillaries, the RBC oxygen saturation and the oxygen-carrying capacity of a RBC at 100% of saturation. Oxygen diffusion from capillary RBC to tissue cell mitochondria is determined by the product of the oxygen gradient from RBC to mitochondria and the diffusion coefficient, times the exchange surface divided by the diffusion distance (d1 and d2) from RBC to mitochondria. A, Blood flow though microcirculation under normovolemic conditions. B, Impaired convection (due to increased venular outflow pressure) and diffusion (increased diffusion distance [d2] between capillary RBC and tissue cells mitochondria).

hydroxyethyl starch (130/0.4) improved sublingual microcirculatory parameters and decreased flow heterogeneity regardless the type of fluid in preload-responsive severe sepsis and septic shock patients within the first 24 h of ICU admission (49). Interestingly, improvements in microcirculation perfusion after volume expansion either by passive leg raising or volume expansion do not seem to be related to RBC rheology as hemoglobin levels remained constant during the study procedures (49).

Dobutamine and vasopressors

Dobutamine is primarily beta-adrenergic agent, but it also has mild vasodilatory effects (50). Thus, dobutamine administration may improve microvascular blood flow by increasing microcirculatory driving pressure (Fig. 2) and by increasing cardiac output (convective transport of oxygen).

Few studies evaluated the effects of dobutamine on the microcirculation of critically ill patients (42, 51, 52). Initial studies suggested that dobutamine could increase skin microvascular (51) and gastric mucosal blood flow (52, 53). In a prospective open-label study with 22 septic shock patients (<48 h of onset), De Backer et al. (42) demonstrated that dobutamine infusion (5 mcg/kg/h during 2 h) improves capillary blood flow. Interestingly, changes in capillary perfusion did not correlate with changes in systemic hemodynamics (cardiac index, MAP or systemic vascular resistance), but were inversely correlated with changes in arterial lactate levels (42).

The effects of different MAP targets on microcirculation and tissue perfusion in septic shock patients were recently revised elsewhere (54). The impact of increasing MAP from 65 mm Hg to 85 mm Hg on microcirculatory blood flow was prospectively evaluated in 20 fluid resuscitated septic shock patients (55). In this study, increasing MAP with escalating doses of norepinephrine failed to improve microvascular blood flow in small, medium, and large vessels (55). Similar findings were reported by Jhanji et al. (56), who demonstrated that escalating doses of norepinephrine aiming to increase MAP from 60 to 70, 80, and 90 mm Hg, respectively, had no effects on sublingual microvascular blood flow in septic shock patients.

Red blood cells transfusion

It was demonstrated in a prospective observational study with 35 severe sepsis and septic shock patients that an increase in hemoglobin concentration from 7.1 g/dL to 8.1 g/dL through a leukocyte-reduced RBC transfusion, failed to improve sublingual microcirculation despite improving DO_2 (57). Similar findings were reported by Sadaka et al. (58), who demonstrated that an increase on hemoglobin concentration from approximately 7.2 g/dL to 8.8 g/dL through one non-leukoreduced packed RBC transfusion during the first 12 h of sepsis did not affect sublingual microcirculation and thenar tissue oxygen saturation (StO_2). Finally, whether non-leukodepleted or leukodepleted RBC transfusion affects the microvascular perfusion in septic patients and whether microcirculation analysis is useful to guide RBC transfusion need to be further investigated (59).

FUTURE DIRECTIONS

Microcirculation analysis in critically ill patients is an evolving issue (1). The development of new user-friendly devices to assess microcirculation at the bedside along with a rapid, online, operator independent, and automated image analysis will allow researchers to explore therapies targeting microcirculation during the early phases of septic shock resuscitation more easily and quickly (60, 61).

Recently, a third generation of handheld microscope, based on Incident Dark Field illumination (IDF) (CytoCam; Braedius Medical BV, Huizen, The Netherlands), along with an automatized analysis software (CytoCamTools V1; Braedius Medical BV, Huizen, The Netherlands), has been launched (60). The CytoCam-IDF imaging provides a better image quality in terms of contrast and image sharpness and has proved effective in detecting 30% more capillaries in health volunteers than Sidestream Dark Field imaging (SDF) due to improved magnification lens and a high-resolution sensor (60). Nevertheless, the accuracy of this new automatized analysis software to detect microvascular abnormalities in septic shock patients needs to be addressed (62).

Finally, so far, no study has evaluated if targeting microcirculation during a quantitative resuscitation algorithm would affect outcomes in septic shock patients. Therefore, new and well-designed studies, adequately powered, addressing the impact of such resuscitation strategy on patient centered outcomes are needed.

CONCLUSIONS

While normalization of macrohemodynamic parameters remains a concern in septic shock resuscitation, it was clearly demonstrated that such parameters poorly reflect the microcirculation condition. Moreover, microcirculatory derangements are frequent in septic shock patients and have been associated with increased morbidity and mortality. Therefore, additional efforts aiming to improve microcirculation, such as intravenous vasodilators administration, have been advocated. However, the impact of such interventions on patient-centered outcomes needs to be further verified through well-designed randomized controlled clinical trials.

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