Microcirculatory Blood Flow as a New Tool for Perioperative Fluid Management

7

Daniel De Backer

Abstract

Microcirculatory alterations often occur in the perioperative setting under the influence of multiple factors including hypovolemia, impaired cardiac function, vasoplegia, anesthetic agents, surgical trauma, ischemia/reperfusion injury and sepsis. The severity and duration of these alterations has been related to the outcome of these patients. This systematic review will report to which extend these microvascular abnormalities can be affected by fluid administration.

Administration of fluids usually improves microvascular dysfunction by increasing the perfused capillary density. Importantly, there is an important variability among the patients. Timing of the intervention has a huge impact as early interventions often led to an improved microvascular perfusion while delayed intervention often fails to improve the microcirculation. Of note the impact of fluids on the microcirculation is relatively dissociated form its systemic effects and can thus not be predicted by changes in cardiac output or blood pressure. Changes in lactate or in veno-arterial PCO2 gradients can be useful to indirectly evaluate the microvascular effects of fluids. Even though colloids are often associated with greater effects than crystalloids in experimental settings, this has not been confirmed in patients. Finally the impact of red blood cell transfusions is highly variable and may depend on the severity of microvascular alterations at baseline.

D. D. Backer (✉)
Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium
e-mail: ddebacke@ulb.ac.be

E. Farag et al. (eds.), *Perioperative Fluid Management*,
https://doi.org/10.1007/978-3-030-48374-6_7

Introduction

Tissue perfusion is often altered in the perioperative setting, as a result of decreased organ perfusion associated to low cardiac output and/or hypotension. However, alterations in microvascular perfusion can also contribute to impaired tissue perfusion and this has only recently been recognized. The severity and duration of these alterations have been related to the development of perioperative organ dysfunction [1].

Fluids are administered in the perioperative setting hoping that the increase in cardiac preload would result in an increased organ perfusion and in tissue perfusion. As microvascular perfusion is relatively independent from systemic perfusion [2–4], the impact of fluids on the microcirculation is not straightforward. We performed a systemic review (Pubmed search April 2019 using the following keywords: fluids, crystalloids, colloids, albumin, starches, hypertonic lactate, transfusions, microcirculation, microvascular, capillary) to discuss how fluids can influence microvascular perfusion.

Characterization of the Microvascular Alterations Observed in the Perioperative Setting

Several types of microvascular alterations may occur in the perioperative setting (Table 7.1). These are due to several factors including bleeding, impaired cardiac function, infection, tissue trauma, ischemia/reperfusion injury which can influence microvascular perfusion in different ways. Of note, multiple factors can of course occur simultaneously and have, sometimes, opposing influences. Accordingly, the incidence, nature, and severity of the microvascular alterations in the perioperative setting will depend on the contribution of these different factors, in conjunction to some predisposing factors related to the host such as advanced age, chronic

Table 7.1 Type of microvascular alteration according to the type of mechanisms

Mechanism	Effector	Microvascular alteration
Bleeding	Low cardiac output leading to impaired organ perfusion	Homogeneous decreased perfusion in all vessels ± decreased vascular density
Cardiac dysfunction		
Vasoplegia	Decreased perfusion pressure leading to impaired organ perfusion	
Anesthetic agents	??	Decreased vascular density/stop flow in some capillaries while others remain well perfused/ heterogeneity between areas
Sepsis	Activation of inflammation and coagulation pathways	
Tissue trauma		
Ischemia/ reperfusion		

Several mechanisms can coincide

cardiovascular diseases, diabetes, cirrhosis,…These factors will also affect the microvascular response to fluids.

Hypovolemia (bleeding) and impaired cardiac function (either pre-existing or induced by anesthetic agents or sepsis) may result in an impaired cardiac output which directly alters perfusion to organs, and especially less vital organs such as muscle, kidney and splanchnic region. Similarly, hypotension, as a result of decreased vascular tone under the influence of anesthetic agents, sepsis or ischemia/reperfusion injury, is also associated with blood flow redistribution among the organs and also results in hypoperfusion of some organs. These alterations are mostly characterized by a homogeneous decrease in perfusion in all microvascular vessels including arterioles and capillaries. One can expect this type of alterations to be sensitive to fluids, provided the heart is preload responsive, or alternatively to inotropes and vasopressors.

Infection and sepsis are associated with activation of inflammation and coagulation that result in diffuse endothelial dysfunction. Sepsis-associated alterations in microvascular perfusion are characterized by a decrease in capillary density and decreased proportion of perfused capillaries leading to heterogeneous tissue perfusion [5–7]. In the perfused vessels flow is usually already quite high and often excessive regarding to oxygen requirements of the perfused area. These kinds of alterations generate pouches of hypoxia in close vicinity to excessively perfused area, associated with explaining the high lactate levels and high venous oxygen saturation. This process is not fixed, as capillary perfusion may change minute by minute, and non-perfused capillaries suddenly become perfused and vice-versa. The capacity of the microcirculation to react to stress conditions is completely blunted. In opposition to normal conditions in which the microcirculation decreases its minimal heterogeneity when submitted to hypovolemia, the heterogeneity further increases in the septic microcirculation, leading to a mismatch between flow and oxygen requirements [8].

Anesthesia, tissue trauma and ischemia/reperfusion injury are associated with similar types of activation of the inflammatory cascade. Accordingly, microvascular alterations similar as those described in sepsis are often encountered, even though usually less severe. Anesthetic agents induce some microcirculatory alterations, usually limited in intensity and rapidly resolving after cessation of the infusion of the anesthetic agent [9]. In patients submitted to cardiac and non-cardiac surgery, we demonstrated that microvascular alterations occur already at the onset of anesthesia, worsen during the surgical procedure and slowly recover afterwards [10]. The severity of these microvascular alterations was related to the type of surgery and was associated with degree of organ dysfunction the day after surgery. In patients with trauma, microvascular alterations were observed after hemodynamic stabilization and their severity was related with organ dysfunction [11]. It is important to realize that the combination of multiple kind of injuries (hypovolemia/inflammation/hypoxemia) can further exacerbate these microvascular alterations. In experimental conditions, the effects of hypovolemia combined with hypoxemia generated more alterations to the intestinal microcirculation that any of these in isolation [12].

To improve these heterogeneous alterations, interventions should be able to recruit the microcirculation rather than increasing flow in the already perfused vessels.

The Risks of Fluid Administration for Microvascular Perfusion

The administration of asanguinous fluids carry the risk induced of hemodilution. The impact of hemodilution on the microcirculation are quite variable. On one hand hemodilution decreases blood oxygen carrying capacity, and this may impair tissue oxygenation. On the other hand it also decreases viscosity which may have opposing effects on microvascular perfusion, depending on the hematocrit level. As resistance to flow is proportional to viscosity of the blood, a decrease in viscosity can be associated with an increased red blood cell velocity. However, maintenance of minimal level of viscosity is also needed to maintain microvessels open. At high hematocrit levels, the decrease in viscosity is associated by a decreased resistance to flow and hence improves perfusion especially at the capillary level [13]. At low hematocrit, the decrease in viscosity may favor vessels collapse and thus impair flow [14].

Due to the increased permeability, administration of fluids can also increase tissue edema. While edema can theoretically increase diffusion distance for oxygen, this effect is usually limited. More importantly, tissue edema may also increase interstitial pressure, especially in the splanchnic organs. Even a minimal increase in interstitial pressure can be associated with an impaired microvascular perfusion and adhesions of white blood cell to the endothelium.

Finally, there is also a risk that fluids administration may impair tissue perfusion by increasing venous pressure. Even though it was reported in one observational trial that a high central venous pressure after fluid resuscitation was associated with an impaired microvascular perfusion in patients with sepsis, it was difficult to separate the impact of the severity of disease from the impact of increased back pressure (as patients with more severe cardiovascular dysfunction also have higher CVP for the same blood volume) [15].

Impact of Fluids on Microvascular Perfusion: What is the Evidence?

Hypovolemia is associated with a decrease in microvascular perfusion. In patients submitted to hemodialysis, fluid withdrawal was associated with microcirculatory alterations that were more prominent in capillaries [16].

In experimental studies, fluid administration resulted in an improvement of microvascular perfusion [17, 18]. In patients submitted to high risk surgery, administration of fluids improved microvascular reactivity [19]. A recent trial demonstrated the simultaneous occurrence of indices of preload responsiveness and

microvascular alterations in patients submitted to major abdominal surgery [20]. Furthermore, correction of hypovolemia improved microvascular perfusion in these patients [20]. In patients with septic shock, fluids administration was usually associated with an improvement in the proportion of perfused capillaries resulting in an increased perfused vascular density [21–24], even though some individual variability in the response was observed. When microvascular perfusion increased, it also decreased heterogeneity between areas [21] further indicating that the diffusive component of the microcirculation markedly improved. It also resulted in a decrease in veno-arterial and ear lobe tissue PCO2 gradients [25], which are indirect markers of microvascular perfusion [26, 27].

As the response to fluids was somewhat variable, it is important to understand what could be the factors predicting a positive microvascular response. One of the factors may be the relative adequacy of the microcirculation at baseline, fluids being more effective when microcirculation is more altered at baseline than when closer to normal [23, 28]. Importantly, the microvascular response in these various studies was often dissociated for the systemic response [21, 22, 24]. The improvement in microvascular perfusion was observed in patients responding or not to fluid challenge by an increase in cardiac output or arterial pressure [21]. On the other hand, patients increasing their cardiac output or blood pressure in response to fluid did not always experienced an increase in microvascular perfusion. Of note, the magnitude of the increase in microvascular perfusion was correlated with the magnitude of the changes in lactate levels (Fig. 7.1), highlighting that microvascular perfusion is the key determinant of tissue perfusion [21]. At the bedside, changes in lactate and

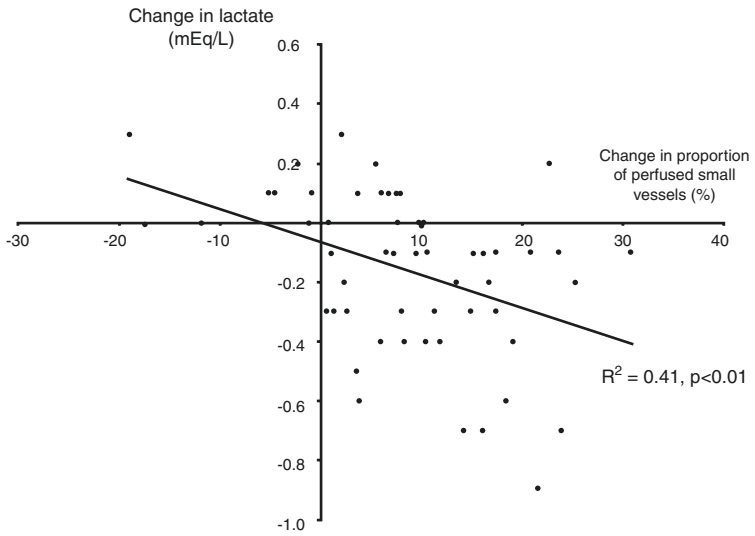

Fig. 7.1 Relationship between changes in microvascular perfusion and changes in lactate levels. Derived from Ospina et al. [21]

veno-arterial PCO2 gradients can thus be used to indirectly evaluate the microvascular response to fluids. Even more importantly, organ function improved the next day in patients experiencing improvements in microvascular perfusion in response to fluids but not in the others [23].

A positive response to fluids may be observed only at early stages of the disease. In experimental sepsis, fluid administration failed to improve the heterogeneity of blood flow distribution when given in a delayed fashion while these were effective at earlier stages [29]. In patients with septic shock, fluids improved microvascular perfusion when administered within 24 h of the onset of sepsis but not after 48 h [21].

Finally, a large amount of fluid is probably not needed. In patients with septic shock, Pottecher et al. [20] showed that the first bolus of fluid improved microvascular perfusion while the second bolus failed, even though it further increased cardiac index. This seems to indicate that the impact of fluid may be saturable.

Colloids Versus Crytalloids

There is an ongoing debate on whether colloids have a greater effect on the microcirculation compared to crystalloids. Theoretically, one may expect that crystalloids may better preserve microvascular perfusion and limit capillary leak, potentially by better preserving the glycocalyx [30–33].

In experimental studies, colloids often increase more significantly microvascular perfusion compared to crystalloids both in ischemia reperfusion injury [33] and in sepsis [17]. In addition, colloids also had a favorable impact on adhesion of white blood cells and platelets to the endothelium [17, 33]. In humans, very few studies compared the impact of colloids to crystalloids on the microcirculation. In 60 patients with septic shock, albumin and Ringer's Lactate similarly improved the sublingual microcirculation [21]. These results contrast with the findings of Dubin et al. [34] who reported that hydroxyethystarch better preserved the sublingual microcirculation of patients with septic shock compared to saline. Of note, the microcirculation was not evaluated at baseline making difficult to differentiate a positive impact of the type of fluid from an imbalance at baseline in this very small series of patients. Another factor may be related to the comparator as the effects of balanced crystalloids may differ from those of saline. In experimental sepsis, balanced solutions ware associated with better preserved microcirculation compared to saline [35]. Half molar lactate may even better protect the endothelium than saline of similar osmolarity, resulting in a better preserved microcirculation [36]. Accordingly, experimental studies almost unanimously point out some beneficial effects of colloids, and especially albumin, over crystalloids on microvascular perfusion, but it is difficult to ascertain that these differences can also be observed in critically ill patients.

Red Blood Cell Transfusions?

Red blood cell transfusions should always be considered as an alternative to asanguinous fluids in order to increase oxygen delivery to the tissues. The main difficulty in predicting the potential impact of red blood cell transfusions is that microvascular hematocrit is lower but not directly proportional to systemic hematocrit. The mandatory plasma layer of a few microns at the surface of endothelial surface represents a greater proportion of vessel volume in small than in large vessels, reported as Farheus effect (Fig. 7.2). In addition, the distribution of hematocrit varies at bifurcations due to kinetic inertia of red blood cells: hematocrit is larger in vessels with a small angles according to originating vessel than in vessels with a larger angle [37] (Fig. 7.3).

While experimental studies often demonstrated an improvement in microvascular perfusion and tissue oxygenation with red blood cell transfusions [38, 39], their effects are more variable in perioperative or septic patients [40–44]. In patients submitted to cardiac surgery, transfusions increased capillary density but not microvascular flow [44]. In another series of postoperative patients the effects of transfusions were more mitigated [43]. In patients with sepsis, there were no effect in most trials [40, 42, 45] while some others found beneficial effects [41]. In patients with trauma, transfusions also were associated with variable effects [46].

Obviously, there is a huge individual variability in the response to red blood cell transfusions, as demonstrated in the trials that reported individual responses, with markedly positive effect in some patients, absence of effects in others, and a markedly negative effect in the remaining patients. The magnitude of the effect is far above the intrinsic variability of the measurements. The direction of the effect may

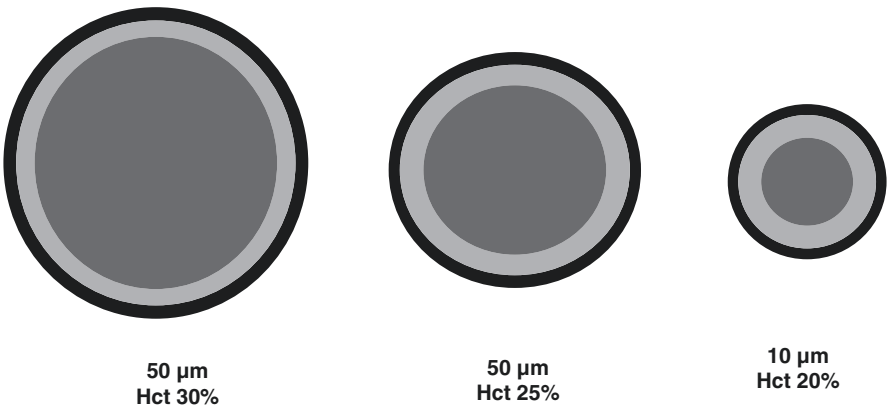

Fig. 7.2 Microvascular hematocrit differs according to the size of the vessel. Due to a mandatory plasma layer of a few microns at the surface of the endothelium, the microvascular hematocrit decreases with vessel size

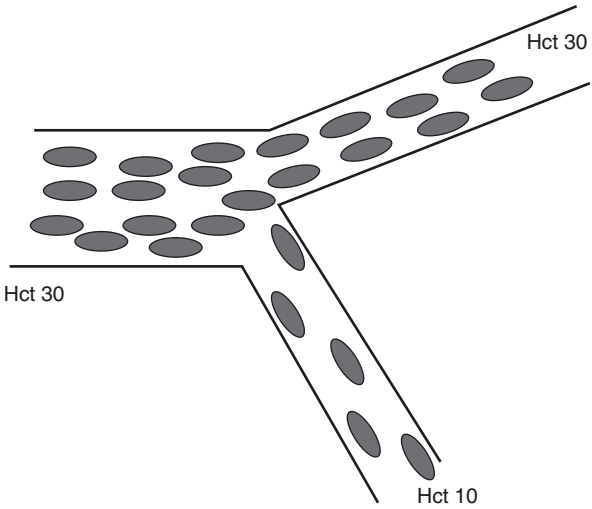

Fig. 7.3 Variability of hematocrit in branch vessels. Due to kinetic inertia of red blood cells, hematocrit is higher in vessels with minimal angle with source vessels compared to vessels with larger angle

depend on the severity of the underlying microcirculatory alterations at baseline, with an improvement in microcirculatory perfusion and tissue oxygenation in patients with alterations in these variables at baseline but also deterioration of these in the patients who had less altered microcirculation variables at baseline [40, 42, 46]. The effects of transfusions on the microcirculation were not related to baseline hemoglobin levels nor with the changes in systemic hemoglobin levels [40, 42].

Based on preclinical observations [38], it has been suggested that transfusions of young red blood cells but not old red blood cell could improve the microcirculation. In a limited size single centre randomized trial in postoperative patients, transfusion of young red blood cells was associated with a greater improvement in microvascular perfusion than when red blood cells older than 3 weeks were transfused [43]. In other trials, the age of red blood cells was not affecting the response to transfusions in critically ill patients [45], after cardiac surgery [47] and in septic patients [40]. Hence, the impact of age of red blood cells on microvascular response remains questionable. Of note this is in accordance with a large randomized clinical trial that failed to demonstrate an impact of the age of red blood cells on outcome, including on organ dysfunction [48].

How Can We Assess the Microcirculation at Bedside?

Videomicroscopic techniques use the reflection by deeper tissue layers to illuminate the tissue to investigate, and several methods to discard the light reflected by superficial layers. Orthogonal polarization spectral (OPS), Sidestream Dark-Field (SDF), and Incident Dark-Field (IDF) are three imaging techniques that can easily be applied at the bedside in critically ill patients. These techniques are mostly used to study the sublingual area [21, 49], which is supposed to reflect other organs when

diffuse alterations are observed, such as in sepsis [5], but may fail to track microcirculatory alterations that may occur to organs submitted to increased interstitial pressure (such as in abdominal compartment syndrome). The use of this technique requires some training and, more importantly, may be difficult to obtain in agitated patients or in patients under noninvasive mechanical ventilation. Evaluation of the microcirculation is often done by semi-quantitative scores [50] which are highly reproducible and often more reliable than currently available semi-automated analysis software [51]. This semi-quantitative analysis can even be reliably performed at bedside by trained nurses [52].

The microcirculation can also be indirectly evaluated. Tissue PCO2 and venoarterial PCO2 gradients are particularly attractive. Tissue PCO2 reflects the balance between CO2 production (and thus metabolism) and perfusion, and therefore can be used to indirectly evaluate tissue perfusion [27]**.** Tissue PCO2 can be measured by contact probes at ear lobe or on the stomach (but gastric tonometry is no more available). Tissue PCO2 measurements can detect zones of impaired perfusion and/or tissue hypoxia even when perfusion is heterogeneous, as the measured value reflects the most abnormal value in the sampled volume. *Venoarterial gradients in PCO2 (PvaCO2) can also be used to evaluate microvascular perfusion. In a series of 75 patients with septic shock in whom sublingual microcirculation and PvaCO2 were measured, a PvaCO2 value greater than 6 mmHg was associated with moderate alterations in sublingual microcirculation and values above 10 mmHg were associated with very severe microvascular alterations. More importantly, changes PvaCO2 were inversely related with changes in microvascular perfusion* [27]. *HencePvaCO2 measurements can thus be used to indirectly assess the microcirculation, especially when venous oxygen saturation is normal.*

Conclusions

Microvascular perfusion is often altered in patients in the perioperative period, especially in high risk surgical patients and in the context of sepsis. Hypovolemia, anesthesia and surgical trauma, in addition to a potential underlying infection, may contribute to microvascular alterations, and hence in alterations in tissue perfusion and oxygenation.

Fluids often improve microvascular perfusion if given early in the course of the disease and this effect is somewhat dissociated form the systemic effects of fluids. The advantage of colloids over crystalloids suggested in experimental studies has not been demonstrated in critically ill patients. The effects of red blood cell transfusions are highly variable and seem to be dependent on the alterations in microcirculation at baseline.

Key Points

- Microvascular alterations frequently occur in the perioperative setting
- Fluids improve functional capillary density but this effect can be variable

- The microvascular effects of fluids cannot be predicted from their systemic effects
- An improvement in microvascular perfusion after fluid administrations is associated with an improvement in organ function
- The impact of red blood cell transfusions is highly variable

References

1. Jhanji S, Lee C, Watson D, Hinds C, Pearse RM. Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications. Intensive Care Med. 2009;35(4):671–7.
2. De Backer D, Creteur J, Dubois MJ, Sakr Y, Koch M, Verdant C, et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med. 2006;34(2):403–8.
3. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med. 2002;166:98–104.
4. Edul VS, Ince C, Vazquez AR, Rubatto PN, Espinoza ED, Welsh S, et al. Similar microcirculatory alterations in patients with Normodynamic and Hyperdynamic septic shock. Ann Am Thorac Soc. 2016;13(2):240–7.
5. Verdant CL, De Backer D, Bruhn A, Clausi C, Su F, Wang Z, et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med. 2009;37:2875–81.
6. Farquhar I, Martin CM, Lam C, Potter R, Ellis CG, Sibbald WJ. Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res. 1996;61:190–6.
7. Secor D, Li F, Ellis CG, Sharpe MD, Gross PL, Wilson JX, et al. Impaired microvascular perfusion in sepsis requires activated coagulation and P-selectin-mediated platelet adhesion in capillaries. Intensive Care Med. 2010;36(11):1928–34.
8. Humer MF, Phang PT, Friesen BP, Allards MF, Goddard CM, Walley KR. Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol. 1996;81:895–904.
9. Koch M, De Backer D, Vincent JL, Barvais L, Hennart D, Schmartz D. Effects of propofol on human microcirculation. Br J Anaesth. 2008;101(4):473–8.
10. De Backer D, Dubois MJ, Schmartz D, Koch M, Ducart A, Barvais L, et al. Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. Ann Thorac Surg. 2009;88(5):1396–403.
11. Tachon G, Harrois A, Tanaka S, Kato H, Huet O, Pottecher J, et al. Microcirculatory alterations in traumatic hemorrhagic shock. Crit Care Med. 2014;42(6):1433–41.
12. Harrois A, Baudry N, Huet O, Kato H, Lohez M, Ziol M, et al. Synergistic deleterious effect of hypoxemia and hypovolemia on microcirculation in intestinal villi*. Crit Care Med. 2013;41(11):e376–e84.
13. Lipowsky HH, Firrel JC. Microvascular hemodynamics during systemic hemodilution and hemoconcentration. Am J Phys. 1986;250:H908–H22.
14. Cabrales P, Martini J, Intaglietta M, Tsai AG. Blood viscosity maintains microvascular conditions during normovolemic anemia independent of blood oxygen-carrying capacity. Am J Physiol Heart Circ Physiol. 2006;291(2):H581–H90.
15. Vellinga NA, Ince C, Boerma EC. Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis. BMC Anesthesiol. 2013;13(1):17.
16. Bemelmans RH, Boerma EC, Barendregt J, Ince C, Rommes JH, Spronk PE. Changes in the volume status of haemodialysis patients are reflected in sublingual microvascular perfusion. Nephrol Dial Transplant. 2009;24:3487–92.

17. Hoffmann JN, Vollmar B, Laschke MW, Inthorn D, Schildberg FW, Menger MD. Hydroxyethyl starch (130 kD), but not crystalloid volume support, improves microcirculation during normotensive endotoxemia. Anesthesiology. 2002;97(2):460–70.
18. de Carvalho H, Dorigo D, Bouskela E. Effects of Ringer-acetate and Ringer-dextran solutions on the microcirculation after LPS challenge: observations in the hamster cheek pouch. Shock. 2001;15:157–62.
19. Futier E, Christophe S, Robin E, Petit A, Pereira B, Desbordes J, et al. Use of near-infrared spectroscopy during a vascular occlusion test to assess the microcirculatory response during fluid challenge. Crit Care. 2011;15(5):R214.
20. Bouattour K, Teboul JL, Varin L, Vicaut E, Duranteau J. Preload dependence is associated with reduced sublingual microcirculation during major abdominal surgery. Anesthesiology. 2019;130(4):541–9.
21. Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Buchele G, Simion D, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med. 2010;36(6):949–55.
22. Pottecher J, Deruddre S, Teboul JL, Georger J, Laplace C, Benhamou D, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. Intensive Care Med. 2010;36:1867–74.
23. Pranskunas A, Koopmans M, Koetsier PM, Pilvinis V, Boerma EC. Microcirculatory blood flow as a tool to select ICU patients eligible for fluid therapy. Intensive Care Med. 2013;39(4):612–9.
24. Klijn E, van Velzen MH, Lima AP, Bakker J, Van BJ GAB. Tissue perfusion and oxygenation to monitor fluid responsiveness in critically ill, septic patients after initial resuscitation: a prospective observational study. J Clin Monit Comput. 2015;29(6):707–12.
25. Vallee F, Mateo J, Dubreuil G, Poussant T, Tachon G, Ouanounou I, et al. Cutaneous ear lobe PCO2 at 37{degrees}C to evaluate micro perfusion in septic patients. Chest. 2010;138(5):1062–70.
26. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006;32(4):516–23.
27. Ospina-Tascon GA, Umana M, Bermudez WF, Bautista-Rincon DF, Valencia JD, Madrinan HJ, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med. 2016;42(2):211–21.
28. Edul VS, Ince C, Navarro N, Previgliano L, Risso-Vazquez A, Rubatto PN, 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.
29. Legrand M, Bezemer R, Kandil A, Demirci C, Payen D, Ince C. The role of renal hypoperfusion in development of renal microcirculatory dysfunction in endotoxemic rats. Intensive Care Med. 2011;37(9):1534–42.
30. Horstick G, Lauterbach M, Kempf T, Ossendorf M, Kopacz L, Heimann A, et al. Plasma protein loss during surgery: beneficial effects of albumin substitution. Shock. 2001;16(1):9–14.
31. Horstick G, Lauterbach M, Kempf T, Bhakdi S, Heimann A, Horstick M, et al. Early albumin infusion improves global and local hemodynamics and reduces inflammatory response in hemorrhagic shock. Crit Care Med. 2002;30(4):851–5.
32. Ngo AT, Jensen LJ, Riemann M, Holstein-Rathlou NH, Torp-Pedersen C. Oxygen sensing and conducted vasomotor responses in mouse cremaster arterioles in situ. Pflugers Arch. 2010;460(1):41–53.
33. Steinbauer M, Guba M, Buchner M, Farkas S, Anthuber M, Jauch KW. Impact of polynitroxylated albumin (PNA) and tempol on ischemia/reperfusion injury: intravital microscopic study in the dorsal skinfold chamber of the Syrian golden hamster. Shock. 2000;14:163–8.
34. Dubin A, Pozo MO, Casabella CA, Murias G, Palizas F Jr, Moseinco MC, et al. Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. J Crit Care. 2010;25:659.e1–8.

35. Orbegozo D, Su F, Santacruz C, He X, Hosokawa K, Creteur J, et al. Effects of different crystalloid solutions on hemodynamics, peripheral perfusion, and the microcirculation in experimental abdominal sepsis. Anesthesiology. 2016;125(4):744–54.
36. Duburcq T, Durand A, Dessein AF, Vamecq J, Vienne JC, Dobbelaere D, et al. Comparison of fluid balance and hemodynamic and metabolic effects of sodium lactate versus sodium bicarbonate versus 0.9% NaCl in porcine endotoxic shock: a randomized, open-label, controlled study. Crit Care. 2017;21(1):113.
37. Fenton BM, Carr RT, Cokelet GR. Nonuniform red cell distribution in 20 to 100 micrometers bifurcations. Microvasc Res. 1985;29(1):103–26.
38. Gonzalez AM, Yazici I, Kusza K, Siemionow M. Effects of fresh versus banked blood transfusions on microcirculatory hemodynamics and tissue oxygenation in the rat cremaster model. Surgery. 2007;141(5):630–9.
39. Kerger H, Waschke KF, Ackern KV, Tsai AG, Intaglietta M. Systemic and microcirculatory effects of autologous whole blood resuscitation in severe hemorrhagic shock. Am J Phys. 1999;276:H2035–H43.
40. Sakr Y, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, et al. Microvascular response to red blood cell transfusion in patients with severe sepsis. Crit Care Med. 2007;35(7):1639–44.
41. Donati A, Damiani E, Luchetti MM, Domizi R, Scorcella C, Carsetti A, et al. Microcirculatory effects of the transfusion of leukodepleted or non-leukodepleted red blood cells in septic patients: a pilot study. Crit Care. 2014;18(1):R33.
42. Sadaka F, Aggu-Sher R, Krause K, O'Brien J, Armbrecht ES, Taylor RW. The effect of red blood cell transfusion on tissue oxygenation and microcirculation in severe septic patients. Ann Intensive Care. 2011;1(1):46.
43. Ayhan B, Yuruk K, Koene S, Sahin A, Ince C, Aypar U. The effects of non-leukoreduced red blood cell transfusions on microcirculation in mixed surgical patients. Transfus Apher Sci. 2013;49(2):212–22.
44. Yuruk K, Almac E, Bezemer R, Goedhart P, de Mol B, Ince C. Blood transfusions recruit the microcirculation during cardiac surgery. Transfusion. 2011;51(5):961–7.
45. Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ, et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med. 2004;32(2):364–71.
46. Tanaka S, Escudier E, Hamada S, Harrois A, Leblanc PE, Vicaut E, et al. Effect of RBC transfusion on sublingual microcirculation in hemorrhagic shock patients: a pilot study. Crit Care Med. 2017;45(2):e154–e60.
47. Stowell CP, Whitman G, Granger S, Gomez H, Assmann SF, Massey MJ, et al. The impact of red blood cell storage duration on tissue oxygenation in cardiac surgery. J Thorac Cardiovasc Surg. 2017;153(3):610–9.
48. Lacroix J, Hebert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. N Engl J Med. 2015;372(15):1410–8.
49. De Backer D, Donadello K, Sakr Y, Ospina-Tascon GA, Salgado DR, Scolletta S, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. Crit Care Med. 2013;41(3):791–9.
50. Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, Duranteau J, et al. 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;44:281–99.
51. Sardinha J, MacKinnon S, Lehmann C. Rapid clinical assessment of the sublingual microcirculation – visual scoring using microVAS in comparison to standard semi-automated analysis. Clin Hemorheol Microcirc. 2018;72(3):229–38.
52. Tanaka S, Harrois A, Nicolai C, Flores M, Hamada S, Vicaut E, et al. Qualitative real-time analysis by nurses of sublingual microcirculation in intensive care unit: the MICRONURSE study. Crit Care. 2015;19:388.