ANESTHESIOLOGY

Preload Dependence Is Associated with Reduced Sublingual Microcirculation during Major Abdominal Surgery

Karim Bouattour, M.D., Jean-Louis Teboul, M.D., Ph.D., Laurent Varin, M.D., Eric Vicaut, M.D., Ph.D., Jacques Duranteau, M.D., Ph.D.

Anesthesiology 2019; 130:541–9

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Whether sublingual microcirculation reflects systemic preload remains unknown

What This Article Tells Us That Is New

- Thirty-two preload dependent episodes were identified in 17 patients
- Episodes were accompanied by reduced arterial pressure and stroke volume, along with reduced sublingual microcirculation
- Fluid administration improved microcirculation and stroke volume, but not blood pressure
- Sublingual microcirculation might be an indicator of vascular volume

ABSTRACT

Background: Dynamic indices, such as pulse pressure variation, detect preload dependence and are used to predict fluid responsiveness. The behavior of sublingual microcirculation during preload dependence is unknown during major abdominal surgery. The purpose of this study was to test the hypothesis that during abdominal surgery, microvascular perfusion is impaired during preload dependence and recovers after fluid administration.

Methods: This prospective observational study included patients having major abdominal surgery. Pulse pressure variation was used to identify preload dependence. A fluid challenge was performed when pulse pressure variation was greater than 13%. Macrocirculation variables (mean arterial pressure, heart rate, stroke volume index, and pulse pressure variation) and sublingual microcirculation variables (perfused vessel density, microvascular flow index, proportion of perfused vessels, and flow heterogeneity index) were recorded every 10 min.

Results: In 17 patients, who contributed 32 preload dependence episodes, the occurrence of preload dependence during major abdominal surgery was associated with a decrease in mean arterial pressure (72 ± 9 *vs.* 83 ± 15 mmHg [mean ± SD]; $P = 0.016$) and stroke volume index (36 ± 8 *vs.* 43 ± 8 ml/m^2; $P < 0.001$) with a concomitant decrease in microvascular flow index (median [interquartile range], 2.33 [1.81, 2.75] *vs.* 2.84 [2.56, 2.88]; $P = 0.009$) and perfused vessel density (14.9 [12.0, 16.4] *vs.* 16.1 mm/mm^2 [14.7, 21.4], $P = 0.009$), while heterogeneity index was increased from 0.2 (0.2, 0.4) to 0.5 (0.4, 0.7; $P = 0.001$). After fluid challenge, all microvascular parameters and the stroke volume index improved, while mean arterial pressure and heart rate remained unchanged.

Conclusions: Preload dependence was associated with reduced sublingual microcirculation during major abdominal surgery. Fluid administration successfully restored microvascular perfusion.

(Anesthesiology 2019; 130:541–9)

Perioperative hemodynamic optimization has proven to improve postoperative outcome in high-risk surgical patients.[1,2] This allows a reduction in the length of stay, mortality, and postoperative complications.[3–5] Fluid administration is the cornerstone of perioperative hemodynamic optimization and is based on the prediction of preload responsiveness. Dynamic indices, such as pulse pressure variation, detect preload dependence and are used to predict fluid responsiveness. Preload dependence is defined as a state in which increases in right ventricular and/or left ventricular end-diastolic volume result in an increase in stroke volume.[6] Nevertheless, while fluid resuscitation guided by dynamic indices leads to optimization of macrocirculation, it remains unclear whether it can improve microcirculation as well. Such improvement can only occur if the physiologic microvascular response is preserved. However, hemorrhagic shock, reperfusion injuries, sepsis, traumatic injuries, and inflammation are conditions known to affect the microcirculatory responses, subsequently leading to a loss of the physiologic relation between macro- and microcirculation. Therefore, in such cases, a systemic hemodynamic-driven resuscitation would not be effective in restoring an adequate microcirculation and tissue oxygenation.[7–12] In this regard, indicators of normal microcirculation should be taken into account by the physician in his evaluation of the

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication February 27, 2018. Accepted for publication December 27, 2018. From the University Hospitals of Paris-Sud, Assistance Publique Des Hôpitaux De Paris, Critical Care and Anesthesia Department, Antoine Béclère Hospital, Clamart, France (K.B.); University Hospitals of Paris-Sud, Assistance Publique Des Hôpitaux De Paris, Medical Intensive Care Unit (J.-L.T.) and Critical Care and Anesthesia Department (L.V., J.D.), Bicêtre Hospital, Le Kremlin Bicêtre, France; and Clinical Research Unit, UMR 942, Lariboisiere University Hospital, Paris, France (E.V.).

<zdoi;10.1097/ALN.0000000000002631>

necessity of fluid resuscitation, even in the case of preload dependence.

Microcirculation monitoring remains limited to a few easily accessible sites. Sublingual microcirculation sequences can be obtained using a handheld vital microscope (sidestream dark field imaging device). This noninvasive technique allows an assessment of microvascular variables such as microvascular flow index, percentage of perfused vessels, perfused vessel density, and heterogeneity index.[13]

Alteration of microvascular perfusion has been closely associated with organ dysfunction and mortality in septic and hemorrhagic shocks.[14–17] Several studies have investigated the relationships between macrovascular hemodynamic optimization and microcirculation in shock. However, very few studies have analyzed the behavior of microcirculation during major surgery.[18–21] To optimize cardiac output and oxygen delivery, hemodynamic management guided by functional assessment of fluid responsiveness is used. Dynamic predictors of fluid responsiveness, namely pulse pressure variation and stroke volume variation, have been shown to be useful in anticipating patients who will respond to a fluid load with a significant increase in stroke volume and cardiac output.[22] Therefore, dynamic predictors of fluid responsiveness are increasingly used to guide fluid therapy. A pulse pressure variation value greater than 13% allows discrimination between responders and nonresponders with a sensitivity of 94% and a specificity of 96%.[23,24] The purpose of this study was to test the hypothesis that during abdominal surgery, microvascular perfusion is impaired during preload dependence, identified by a pulse pressure variation greater than 13%, and recovers after fluid administration.

Materials and Methods

This prospective study was conducted in the Department of Anesthesiology and Critical Care of the University Hospital of Bicêtre, Le Kremlin Bicêtre, France.

Patients

This observational study was approved by our local Institutional Review Board (Protection of Persons Committee, University Hospital of Bicêtre; 2013-A01277-38). Patients of the study were treated in accordance with the local care protocols. Examination of the sublingual microcirculation with a sidestream dark field imaging device is completely noninvasive and respects the noninterventional study design.

Selection of patients was done during anesthesia consultation. Included patients planned for an abdominal surgery of 90 min or greater and the anesthetist deemed the implementation of an arterial catheter necessary to monitor blood pressure based on their condition and the risk of hemodynamic instability during surgery. Oral and written information was given to each patient.

Patients were excluded for any of the following reasons: surgical duration of less than 90 min, laparoscopy, nonsinus cardiac rhythm, end-stage heart failure, pregnancy, age less than 18 yr, contraindication to arterial catheterization (Allen test positive or inconclusive), and impossible access to the patient's head during surgery.

Methods

Patient Characteristics. All cardiovascular, respiratory, and neurologic comorbidities, American Society of Anesthesiologists and New York Heart Association scores, usual medications, clinical abnormalities, and results of preoperative diagnostic tests were recorded on the anesthesiology report.

Macrocirculation Monitoring. All patients were treated in accordance with local care protocols. The pulse pressure variation is routinely used as a marker to detect preload dependence,[25] and a pulse pressure variation value of 13% allows discrimination between responders and nonresponders with a sensitivity of 94% and a specificity of 96%.[23] Every 10 min, the following parameters were collected and recorded on the monitoring report: cardiac index, stroke volume index measured using the Flotrac-Vigileo device (Edwards Lifesciences, USA), pulse pressure variation, heart rate, mean arterial pressure, pulse oxygen saturation, respiratory rate, temperature measured from the Philips IntelliVue Monitoring (Philips Medical Systems, USA), Bispectral Index, inspired and expired oxygen, carbon dioxide, volatile anesthetic fractions, and tidal volume (V_T).

Sublingual Microcirculation Monitoring. Videos of the sublingual microcirculation were obtained using a sidestream dark field imaging device (Microscan, MicroVisionMedical, The Netherlands), a technique derived from the orthogonal polarized spectral imaging technology.[26] Intraoperative sublingual video allowed direct visualization of sublingual blood flow in microvascular networks. The emitted light, corresponding to the hemoglobin wavelength absorption, displays each erythrocyte in black on a light background. Images acquisition and analysis were performed according to international guidelines.[13] The greatest care was provided in order to avoid pressure artifacts in accordance with the published recommendations.[13] Sequence quality was systematically evaluated using the "Microcirculation Image Quality Score" described by Massey *et al.*[27] Poor quality sequences were therefore eliminated at the bedside of the patient, and another sequence was performed to have two good quality sequences for each measurement point. Patient identity and video identification were hidden and replaced by an alphanumeric code assigned randomly, allowing a blinded analysis.

During the surgery, two 10- to 15-s video sequences were acquired every 10 min using the sidestream dark field imaging device by an investigator who was not involved in the patient's care. No real-time on-site analysis of videos

was done. No decision concerning the management of the patient was made on the basis of microcirculatory data acquired during the surgery.

According to the consensus,[13,28] a retrospective analysis of these videos was performed by a second investigator, using a dedicated software (Automated Vascular Analysis ver. 1.0; Academic Medical Center, University of Amsterdam, The Netherlands). We have considered the average values of three sites for each timepoint. Considering the beginning of the fluid challenge, four set of measurements have been considered: the video sequence before the fluid challenge, the two video sequences that preceded this one (*i.e.*, 10 min and 20 min before), and the video sequence after the fluid challenge.

Four microcirculatory parameters have been analyzed (illustrative examples of videos of normal and impaired microcirculatory flow appear in the Supplemental Digital Content 1, http://links.lww.com/ALN/B902, and Supplemental Digital Content 2, http://links.lww.com/ALN/B903, respectively.):

1. The microvascular flow index, which is a qualitative evaluation of the microvascular flow. The image is divided into four quadrants, and the predominant type of flow in very small vessels (*i.e.*, diameter less than 20 μm) is assessed in each quadrant using an ordinal score (0 = no flow, 1 = intermittent flow, 2 = sluggish flow, 3 = normal flow). The overall score, called microvascular flow index, is the sum of each quadrant score divided by the number of quadrants.[13,28]
2. The percentage of perfused vessels, which is calculated as follows: 100 × (total number of vessels − [no flow + intermittent flow])/total number of vessels.
3. The perfused vessel density (which can also be referred to as functional capillary density), which is calculated automatically by dividing the area of perfused vessels by the total area of interest using the Automated Vascular Analysis software.
4. The heterogeneity index, which is calculated as follows: (highest site microvascular flow index − lowest site microvascular flow index) divided by the mean of the microvascular flow index of all sublingual sites.

Clinical Management

Anesthesia was performed according to our local protocol. Propofol was used as the induction agent, and then sevoflurane or desflurane were used for maintenance. Intravenous sufentanil was used for intraoperative analgesia. Atracurium or succinylcholine was used for intubation. Atracurium boluses were administered thereafter during the surgery. The minimum sevoflurane or desflurane inspired concentration was used according to the Bispectral Index. Sevoflurane or desflurane inspired concentration was left unchanged during fluid challenges. Intraoperative fluid management consisted of a basal infusion of lactated Ringer's solution at a rate of $4\,ml \cdot kg^{-1} \cdot h^{-1}$ to cover evaporative losses and basal fluid requirements. The local hemodynamic protocol was based on pulse pressure variation, cardiac index, and mean arterial pressure[29,30] (Supplemental Digital Content 3; http://links.lww.com/ALN/B901). Preload was optimized by fluid administration until a value of pulse pressure variation less than 13% was obtained. Fluid challenge was performed using a volume of 500 ml of isotonic saline solution (0.9%) in less than 10 min. If the cardiac index value was less than $2.5\,l \cdot min^{-1} \cdot m^{-2}$ without any improvement after fluid challenge, dobutamine was administered to reach this minimum cardiac index value. If pulse pressure variation and cardiac output were within the target range but mean arterial pressure was still less than 65 mmHg, norepinephrine was administered. Concerning the ventilator settings, the V_T was set at $8\,ml/kg^{-1}$ of ideal body weight and the respiratory rate were set to keep end-tidal carbon dioxide between 36 and 41 mmHg. The following pulse pressure variation validity criteria were used: regular cardiac rhythm (no arrhythmia or extrasystoles), controlled mechanical ventilation in the absence of spontaneous breathing and with V_T values between 8 and $10\,ml/kg^{-1}$ of ideal body weight and absence of acute cor pulmonale.

Statistical Analysis

A sample size equal to n = 17 patients was chosen to provide an 80% power to detect by a Wilcoxon test any change in microvascular parameter associated to preload dependence with a standardized effect size equal to 1 with a nominal *P* value at 0.0166. The methods of Shieh *et al.*[31] were used for regarding power calculation. Considering the pilot nature of the current study, we did not adjust the four parameters tested for multiple comparisons, but for each parameter, Bonferonni correction for multiple comparisons was used to test difference between times, and a nominal *P* value less than 0.0166 was required to claim statistical significance.

Changes in micro- and macrovascular parameters were analyzed 20 min and 10 min before, at the time of the preload dependence, and after fluid challenge completion. For those patients with more than one preload dependence episode, these episodes were averaged. The variations with time of the microvascular parameters (microvascular flow index, percentage of perfused vessels, perfused vessel density, and heterogeneity index) and macrovascular parameters (mean arterial pressure, pulse pressure variation, heart rate, and stroke volume index) were analyzed by comparing the values corresponding to the time of preload dependence with the three other times recorded using *t* test for matched pairs for macrovascular parameters with Gaussian distribution (macrovascular parameters) or Wilcoxon signed-rank test for microvascular parameters that have non-Gaussian distribution. To estimate correlation between microvascular parameters and pulse pressure variation or stroke volume index, we used a mixed model for assessing correlation in the presence of replication[32] after rank transformation since data were collected at several times for the same patients and since microvascular parameters were non-Gaussian. All results are shown as mean ± SD for variables with Gaussian

distributions and median (interquartile range) for variables with non-Gaussian distributions. Tests were performed using SAS version 9.4 (SAS Institute, USA).

Results

Demographic Data

Seventeen consecutive patients were included in the study over a 3-month period (flow chart in Supplemental Digital Content 3, http://links.lww.com/ALN/B901). Every patient agreed to participate in the study after oral and written information. Among the 17 patients, one patient did not receive any fluid challenge and was therefore excluded.

Mean age was 59 ± 21 yr, mean American Society of Anesthesiologists score was 2 ± 1 and mean New York Heart Association score was 2 (±1). Patients' demographic data are reported in Supplemental Digital Content 3, Table 1, http://links.lww.com/ALN/B901.

Macrovascular Variables

Preload dependence episodes occurred 32 times. Thirty-two fluid challenges were consequently performed. The median number of fluid challenges per patient was 2 ± 1 (distribution of preload dependence episodes in the Supplemental Digital Content 3, http://links.lww.com/ALN/B901). The average total volume of fluid received per patient was 1,678 ± 1,027 ml. No patient received norepinephrine or erythrocytes during the surgery. Occurrence of preload dependence was concomitant with a significant reduction of the mean arterial pressure from 83 ± 15 mmHg 20 min before fluid challenge to 72 ± 9 mmHg at the time of fluid challenge ($P = 0.016$) and stroke volume index 43 ± 8 ml/m^2 20 min before fluid challenge to 36 ± 8 ml/m^2 at the time of fluid challenge ($P < 0.001$) with no significant change in heart rate (figs. 1 and 3). Fluid challenge significantly decreased pulse pressure variation with an increase in stroke volume index and had no effects on mean arterial pressure and heart rate (fig. 1).

Microvascular Variables

As shown in figures 2 and 3, most of the microvascular parameters decreased significantly during the preload dependence episodes. Microvascular flow index decreased from a median (interquartile range) of 2.8 (2.6, 2.9) 20 min before fluid challenge to 2.3 (1.8, 2.8) at the time of fluid challenge ($P = 0.009$), and perfused vessel density from 16.9 mm/mm^2 (14.7, 21.4) to 14.9 mm/mm^2 (12.0, 16.4; $P = 0.009$), while heterogeneity index was increased from 0.2 (0.2, 0.4) to 0.5 (0.4, 0.7; $P = 0.001$). Percentage of perfused vessels changed from 91.6% (86.1, 97.8) to 76.5% (66.1, 94.0) and did not reach the significance level adjusted

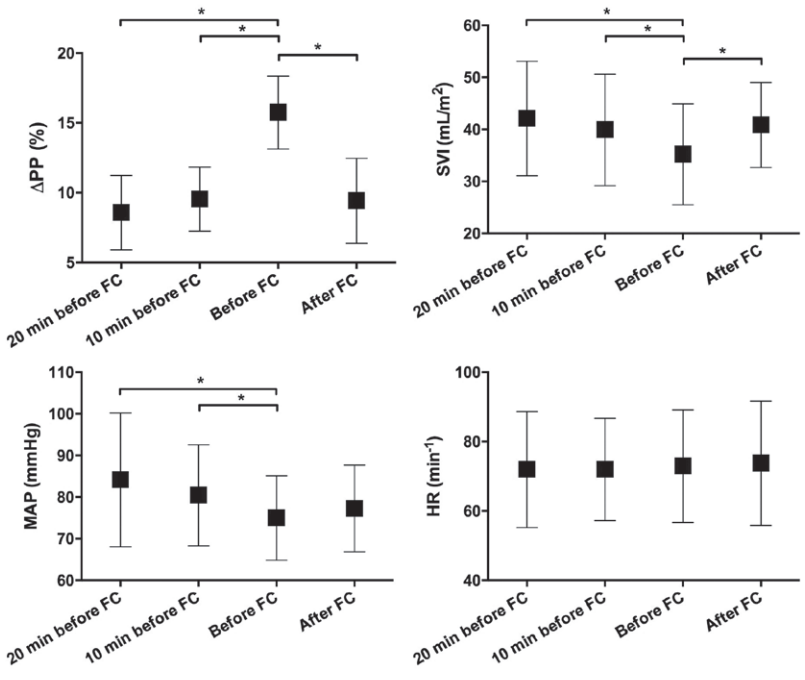

Fig. 1. Mean and SD of pulse pressure variation (Δ PP,%), stroke volume index (SVI, ml/m^2), mean arterial pressure (MAP, mmHg), and heart rate (HR, min^{-1}) 20 and 10 min before preload dependence, at the time of preload dependence, and after fluid challenge (FC) completion (n = 16 patients). For those patients with more than one episode, these episodes were averaged. Sixteen patients had preload dependence episodes. Thirty-two preload dependence episodes were included. *$P < 0.0166$.

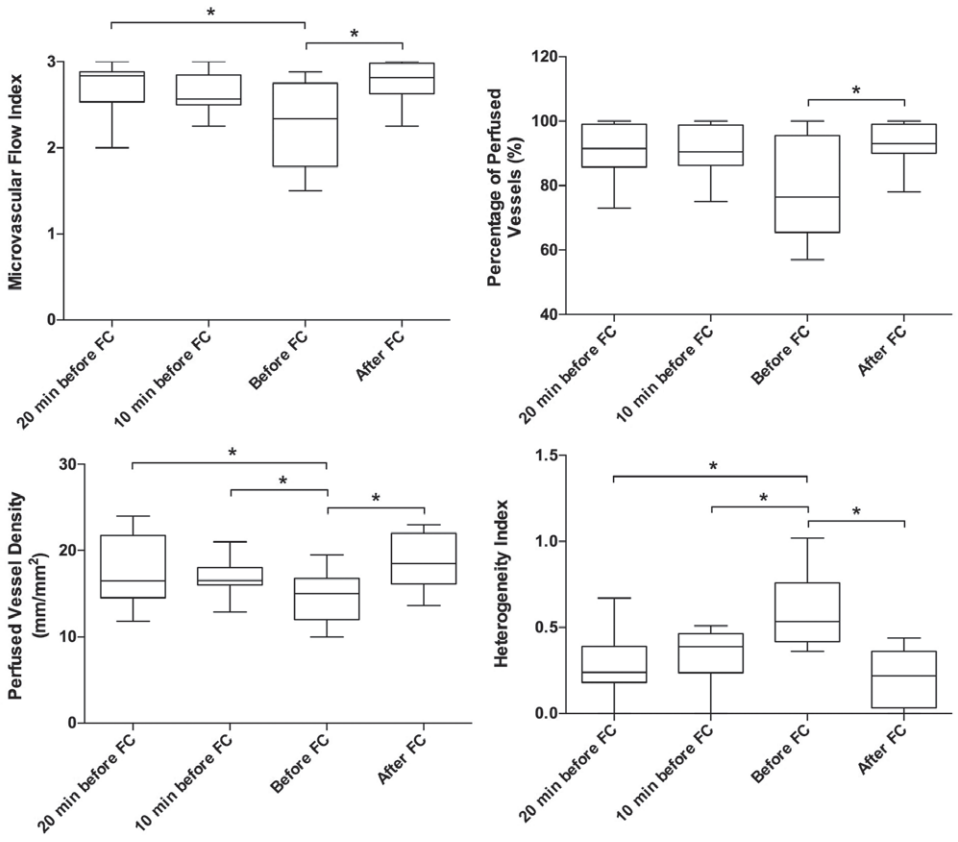

Fig. 2. Median, 25th to 75th percentiles and minimum to maximum values of microvascular flow index, proportion of perfused vessels (%), heterogeneity index, and perfused vessel density (mm/mm^2) 20 and 10 min before preload dependence, at the time of preload dependence, and after fluid challenge (FC) completion (n = 16 patients). For those patients with more than one episode, these episodes were averaged. Sixteen patients had preload dependence episodes. Thirty-two preload dependence episodes were included. *$P < 0.0166$.

for multiplicity. After fluid challenge, all microvascular parameters changed significantly: the microvascular flow index increased to 2.8 (2.6, 3.0; $P = 0.009$), the percentage of perfused vessels increased to 92.9% (89.8, 99.4; $P < 0.002$), and the perfused vessel density increased to 18.6 mm/mm^2 (16.2, 21.8; $P < 0.001$), while the heterogeneity index significantly decreased to 0.2 (0.1, 0.4; $P < 0.001$). Note that when considering values 10 min before fluid challenge, before fluid challenge, and after fluid challenge, microvascular flow index, perfused vessel density, and heterogeneity index were significantly correlated to pulse pressure variation values (r = –0.253, $P = 0.041$; r = –0.310, $P = 0.013$; r = 0.317, $P = 0.001$, respectively). There was no significant correlation between mean arterial pressure or stroke volume index and microvascular parameters.

Discussion

Our findings suggest that sublingual microcirculation was reduced when preload dependence (pulse pressure variation greater than 13%) occurred during major abdominal surgery. Indeed, sublingual microcirculatory variables such as microvascular flow index and perfused vessel density were significantly decreased when preload dependence occurred. Fluid challenge decreased pulse pressure variation and restored microvascular variables but did not restore mean arterial pressure.

In the current study, only sublingual microcirculation was observed, but several studies demonstrated that sublingual microcirculatory changes were correlated to gut[33–37] and renal[38,39] microcirculatory changes. In a large animal model of sepsis, the severity and the time course of microcirculatory changes were similar in sublingual and intestinal microcirculation.[33] Similar results were reported in a sheep model of hemorrhagic shock.[36] de Bruin *et al.* have reported in patients undergoing elective gastrointestinal surgery that gut serosal microvascular imaging with a sidestream dark field device is similar to sublingual assessment.[37] Recently, Lima *et al.*,[39] in a lipopolysaccharide-induced shock model, demonstrated that sublingual microcirculation could reflect renal microvascular alterations detected by contrast-enhanced ultrasonography during shock and

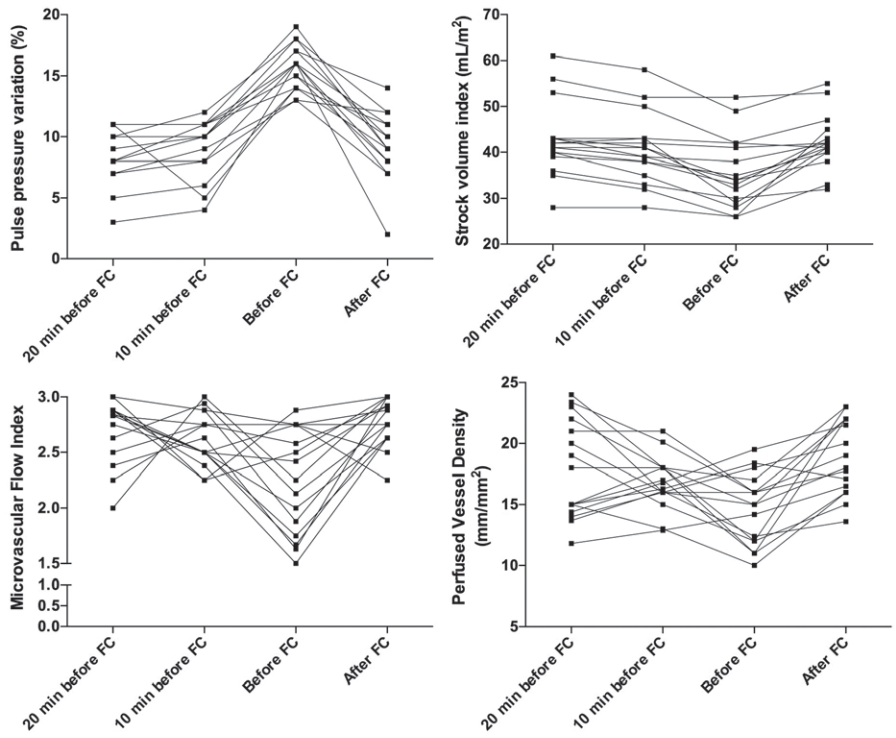

Fig. 3. Individual values of pulse pressure variation (%), stroke volume index (ml/m^2), microvascular flow index, and perfused vessel density (mm/mm^2) 20 and 10 min before preload dependence, at the time of preload dependence, and after fluid challenge completion (n = 16 patients). For those patients with more than one episode, these episodes were averaged. Sixteen patients had preload dependence episodes. Thirty-two preload dependence episodes were included. *$P < 0.0166$.

fluid resuscitation. These results support our belief that the sublingual microcirculation is representative of microcirculation of other organs and especially of vital organs.

The current study assessed the relationship between preload dependence, which refers to the ability of the heart to change its stroke volume in response to a change in its preload, and the sublingual microcirculation during major abdominal surgery. The goal of fluid resuscitation is to restore or maintain oxygen delivery to the tissues. The patterns of microcirculation are difficult to predict solely on the basis of changes in macrocirculatory variables. Indeed, in the context of decreased cardiac output, the physiologic microvascular response primarily aims to preserve tissue perfusion. However, it has been demonstrated that microcirculation could be still altered despite optimization of macrocirculation in shock.[40] This is due to specific microcirculation alterations observed during shock such as viscosity changes, endothelial dysfunction, and glycocalyx or erythrocytes alterations.[41] The degree of microcirculatory alterations may vary with the intensity of shock and of inflammation and may also vary over time. In this regard, in the early phase of septic shock, improvement of microcirculation was observed after fluid infusion, whereas in the late phase of septic shock, optimization of macrocirculation was not always associated with improvement in microcirculation.[42] Persistence of sublingual microcirculatory disorders over time was shown to be associated with a poor outcome.[14–16,43]

In our study, sublingual microcirculatory variables were assessed in patients without prior hemodynamic instability and microvascular impairment. It is interesting to note that sublingual microcirculation was impaired when episodes of preload dependence occurred, which were associated with significant decreases in stroke volume index and mean arterial pressure. With the observed alterations of sublingual microcirculation being contemporaneous with increases in pulse pressure variation (greater than 13%), we can link them to changes in preload. These changes in preload could be due to hypovolemia and/or to a decrease in venous tone with venous dilation. The fact that fluid challenge was able to restore microcirculatory alterations pleads for hypovolemia. Simultaneous changes in stroke volume index and sublingual microcirculatory variables during episodes of preload dependence as well as during fluid challenges suggest there was no dissociation between microcirculation and microcirculation at the level of the sublingual territory. Whether this is related to the use of anesthetic drugs cannot be elucidated by our study.

Our study suggests that episodes of preload dependence have an impact on sublingual microcirculation (and maybe on other sites) during major abdominal surgery. It is important to realize that the presence of fluid responsiveness is not an absolute indication to give fluids. The decision to administer fluid therapy must be supported by the need for hemodynamic improvement. The fact that microvascular alterations were concomitant with episodes of preload dependence is an additional argument to guide fluid resuscitation using dynamic variables (especially pulse pressure variation)[30] and suggests that it is important to correct preload dependence occurring during surgery to avoid microvascular alterations. However, when pulse pressure variation cannot be used (arrhythmia, V_T values less than 8 ml/kg^{-1} of ideal body weight, spontaneous breathing, or acute cor pulmonale) or when pulse pressure variation value is in the gray zone (between 9% and 13%), microvascular sublingual parameters could serve as additional indicators when deciding to administer fluids. Carbon dioxide monitoring appears to be another potential approach. Ospina-Tascón *et al.* have reported that venous-to-arterial carbon dioxide difference could reflect the adequacy of microvascular blood flow.[44] Use of sublingual carbon dioxide monitoring is still to be validated.[45]

The fact that we observed no change in mean arterial pressure after fluid challenge in spite of correction of stroke volume index suggests that a change in arterial tone occurred during fluid challenge. In critically ill patients with septic shock, fluid administration significantly reduced arterial load (*i.e.*, the external opposition that must be overcome by the ventricles during ejection), even when increasing cardiac output.[45] This explains the increase in cardiac output after fluid administration with no improvement in blood pressure for some septic patients. Monge García *et al.* reported on septic shock that in a preload responder group, only 44% of the patients were pressure responders.[46] This fluid-induced reduction in arterial load may have resulted from (1) vasoplegia induced by anesthetic drugs, (2) change in arterial tone due to inflammation, (3) reduction of arterial tone *via* flow-mediated vascular relaxation induced by fluid administration (increase of nitric oxide production and endothelial shear stress), and (4) recruitment of previously closed vessels with an increase of the effective diameter of arterial system and, consequently, reduction in arterial resistance.

Nevertheless, our observational study has several limits. The retrospective microvascular analysis was conducted by a blinded investigator, but video acquisition was performed by a nonblinded investigator. Moreover, it can be argued that the number of patients included in this study is too small to make any conclusion. In addition, it should be stressed that since this is a pilot study, the absence of significant differences for some study parameters may be due to the small sample size. Most patients received β blockers or calcium blockers (which reflects real life), which can have an impact on the observed results. However, we observed no differences between patients treated by each of these drugs and those not receiving them. But we compared small numbers of patients. As angiotensin-converting enzyme inhibitors were stopped 24 h before surgery, their impact can be minimal. We cannot assess with our data the impact of β blockers and calcium blockers on the observed response.

Conclusions

Preload dependence was associated with reduced sublingual microcirculation during major abdominal surgery. Fluid administration successfully restored microvascular perfusion. This finding suggests immediate correction of preload dependence to avoid reduced microcirculation. In the future, microvascular sublingual parameters could serve as additional indicators when deciding to administer fluids.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Duranteau: jacques.duranteau@aphp.fr.

References

1. Hamilton MA, Cecconi M, Rhodes A: A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg 2011; 112:1392–402
2. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care Lond Engl 2005; 9:R687–93
3. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM: Perioperative fluid management strategies in major surgery: A stratified meta-analysis. Anesth Analg 2012; 114:640–51
4. Kern JW, Shoemaker WC: Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002; 30:1686–92

5. Phan TD, Ismail H, Heriot AG, Ho KM: Improving perioperative outcomes: Fluid optimization with the esophageal Doppler monitor, a metaanalysis and review. J Am Coll Surg 2008; 207:935–41
6. Monnet X, Marik PE, Teboul JL: Prediction of fluid responsiveness: An update. Ann Intensive Care 2016; 6:111
7. Dyson A, Cone S, Singer M, Ackland GL: Microvascular and macrovascular flow are uncoupled in early polymicrobial sepsis. Br J Anaesth 2012; 108:973–8
8. Raat NJ, Ince C: Oxygenating the microcirculation: The perspective from blood transfusion and blood storage. Vox Sang 2007; 93:12–8
9. Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Büchele G, Simion D, Chierego ML, Silva TO, Fonseca A, Vincent JL, De Backer D: Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med 2010; 36:949–55
10. Jhanji S, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM: Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: A randomised controlled trial. Crit Care 2010; 14:R151
11. Hiltebrand LB, Krejci V, Sigurdsson GH: Effects of dopamine, dobutamine, and dopexamine on microcirculatory blood flow in the gastrointestinal tract during sepsis and anesthesia. Anesthesiology 2004; 100:1188–97
12. 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; 39:612–9
13. De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, Dobbe I, Ince C: How to evaluate the microcirculation: Report of a round table conference. Crit Care 2007; 11:R101
14. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM; Microcirculatory Alterations in Resuscitation and Shock Investigators: Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 2007; 49:88–98, 98.e1–2
15. Trzeciak S, McCoy JV, Phillip Dellinger R, Arnold RC, Rizzuto M, Abate NL, Shapiro NI, Parrillo JE, Hollenberg SM; Microcirculatory Alterations in Resuscitation and Shock (MARS) investigators: Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 2008; 34:2210–7
16. Genderen ME van, Lima A, Akkerhuis M, Bakker J, Bommel J van: Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012; 40:2287–94
17. Tachon G, Harrois A, Tanaka S, Kato H, Huet O, Pottecher J, Vicaut E, Duranteau J: Microcirculatory alterations in traumatic hemorrhagic shock. Crit Care Med 2014; 42:1433–41
18. Stens J, de Wolf SP, van der Zwan RJ, Koning NJ, Dekker NA, Hering JP, Boer C: Microcirculatory perfusion during different perioperative hemodynamic strategies. Microcirculation 2015; 22:267–75
19. Bansch P, Flisberg P, Bentzer P: Changes in the sublingual microcirculation during major abdominal surgery and post-operative morbidity. Acta Anaesthesiol Scand 2014; 58:89–97
20. Chiarandini P, Pompei L, Costa MG, Vetrugno L, Ronga F, Contin R, Rosa F, Della Rocca G: Effects of catecholamines on microcirculation during general inhalation anesthesia. J Cardiothorac Vasc Anesth 2013; 27:1239–45
21. Prestes I, Riva J, Bouchacourt JP, Kohn E, López A, Hurtado FJ: Microcirculatory changes during cardiac surgery with cardiopulmonary bypass. Rev Esp Anestesiol Reanim 2016; 63:513–8
22. Benes J, Giglio M, Brienza N, Michard F: The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: A meta-analysis of randomized controlled trials. Crit Care 2014; 18:584
23. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000; 162:134–8
24. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, Tavernier B: Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: A "gray zone" approach. Anesthesiology 2011; 115:231–41
25. Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F: Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: A pilot randomized controlled trial. Crit Care 2007; 11:R100
26. Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ, Messmer K, Nadeau RG: Orthogonal polarization spectral imaging: A new method for study of the microcirculation. Nat Med 1999; 5:1209–12
27. Massey MJ, Larochelle E, Najarro G, Karmacharla A, Arnold R, Trzeciak S, Angus DC, Shapiro NI: The microcirculation image quality score: Development and preliminary evaluation of a proposed approach to grading quality of image acquisition for bedside videomicroscopy. J Crit Care 2013; 28:913–7
28. Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, Duranteau J, Pinsky MR, Artigas A, Teboul JL, Reiss

IKM, Aldecoa C, Hutchings SD, Donati A, Maggiorini M, Taccone FS, Hernandez G, Payen D, Tibboel D, Martin DS, Zarbock A, Monnet X, Dubin A, Bakker J, Vincent JL, Scheeren TWL; 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; 44:281–99

29. Salzwedel C, Puig J, Carstens A, Bein B, Molnar Z, Kiss K, Hussain A, Belda J, Kirov MY, Sakka SG, Reuter DA: Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: A multi-center, prospective, randomized study. Crit Care 2013; 17:R191
30. Navarro LH, Bloomstone JA, Auler JO Jr, Cannesson M, Rocca GD, Gan TJ, Kinsky M, Magder S, Miller TE, Mythen M, Perel A, Reuter DA, Pinsky MR, Kramer GC: Perioperative fluid therapy: A statement from the international Fluid Optimization Group. Perioper Med (Lond) 2015; 4:3
31. Shieh G, Jan S-L, Randles RH: Power and sample size determinations for the Wilcoxon signed-rank test. J Stat Comput Simul 2007; 77:717–24
32. Hamlett A, Ryan L, Serrano-Trespalacios P, Wolfinger R: Mixed models for assessing correlation in the presence of replication. J Air Waste Manag Assoc 2003; 53:442–50
33. Verdant CL, De Backer D, Bruhn A, Clausi CM, Su F, Wang Z, Rodriguez H, Pries AR, Vincent JL: Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med 2009; 37:2875–81
34. Pranskunas A, Pilvinis V, Dambrauskas Z, Rasimaviciute R, Planciuniene R, Dobozinskas P, Veikutis V, Vaitkaitis D, Boerma EC: Early course of microcirculatory perfusion in eye and digestive tract during hypodynamic sepsis. Crit Care 2012; 16:R83
35. Jacquet-Lagrèze M, Allaouchiche B, Restagno D, Paquet C, Ayoub JY, Etienne J, Vandenesch F, Dauwalder O, Bonnet JM, Junot S: Gut and sublingual microvascular effect of esmolol during septic shock in a porcine model. Crit Care 2015; 19:241
36. Dubin A, Pozo MO, Ferrara G, Murias G, Martins E, Canullán C, Canales HS, Kanoore Edul VS, Estenssoro E, Ince C: Systemic and microcirculatory responses to progressive hemorrhage. Intensive Care Med 2009; 35:556–64
37. de Bruin AF, Kornmann VN, van der Sloot K, van Vugt JL, Gosselink MP, Smits A, Van Ramshorst B, Boerma EC, Noordzij PG, Boerma D, van Iterson M: Sidestream dark field imaging of the serosal microcirculation during gastrointestinal surgery. Colorectal Dis 2016; 18:O103–10
38. Sui F, Zheng Y, Li WX, Zhou JL: Renal circulation and microcirculation during intra-abdominal hypertension in a porcine model. Eur Rev Med Pharmacol Sci 2016; 20:452–61
39. Lima A, van Rooij T, Ergin B, Sorelli M, Ince Y, Specht PAC, Mik EG, Bocchi L, Kooiman K, de Jong N, Ince C: Dynamic contrast-enhanced ultrasound identifies microcirculatory alterations in sepsis-induced acute kidney injury. Crit Care Med 2018; 46:1284–92
40. De Backer D, Ortiz JA, Salgado D: Coupling microcirculation to systemic hemodynamics. Curr Opin Crit Care 2010; 16:250–4
41. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL: Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5:73–9
42. Pottecher J, Deruddre S, Teboul JL, Georger JF, Laplace C, Benhamou D, Vicaut E, Duranteau J: 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
43. De Backer D, Donadello K, Sakr Y, Ospina-Tascon G, Salgado D, Scolletta S, Vincent JL: Microcirculatory alterations in patients with severe sepsis: Impact of time of assessment and relationship with outcome. Crit Care Med 2013; 41:791–9
44. Ospina-Tascón GA, Umaña M, Bermúdez WF, Bautista-Rincón DF, Valencia JD, Madriñán HJ, Hernandez G, Bruhn A, Arango-Dávila C, De Backer D: Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016; 42:211–21
45. Fox BD, Joyal D, Schlesinger RD, Eisenberg MJ, Langleben D: Evaluation of the Microstat™ sublingual PCO2 monitor in ambulatory patients. J Clin Monit Comput 2016; 30:77–80
46. Monge García MI, Guijo González P, Gracia Romero M, Gil Cano A, Oscier C, Rhodes A, Grounds RM, Cecconi M: Effects of fluid administration on arterial load in septic shock patients. Intensive Care Med 2015; 41:1247–55