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Published in:
Journal of cardiothoracic and vascular anesthesia

DOI:
10.1053/j.jvca.2019.10.038

Publication date:
2020

Journal of Cardiothoracic and Vascular Anesthesia 34 (2020) 2754–2765

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Review Article

Monitoring of the Sublingual Microcirculation During Cardiac Surgery: Current Knowledge and Future Directions

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Handheld vital microscopes allow for direct observation of the sublingual microcirculatory perfusion during cardiac surgery. Through the use of handheld vital microscopes, it has been shown that cardiac surgery with cardiopulmonary bypass is associated with reduced and heterogenous microcirculatory perfusion. Microcirculatory impairment can result in inadequate tissue perfusion, leading to perioperative complications and poor outcome. Because microcirculatory impairment can occur despite stable or improved global hemodynamics, there is a yet unmet need for specific monitoring of the microcirculation. Technological advancements may facilitate point-of-care monitoring of microcirculatory perfusion using automated real-time analysis of microcirculatory measurements. Thus, microcirculatory monitoring may create new opportunities for specific microcirculatory treatment as part of hemodynamic management. The implementation of microcirculatory variables into personalized treatment concepts has the potential to improve hemodynamic management during cardiac surgery and thereby improve patient outcomes. Therefore, specific treatment strategies need to be developed to prevent or treat alterations of the microcirculatory perfusion. In the future, the use of handheld vital microscopes for microcirculatory monitoring may help to improve hemodynamic management and outcomes for patients undergoing cardiac surgical procedures.

Key Words: microvascular flow index; microcirculatory monitoring; microcirculatory perfusion; capillary perfusion; cardiothoracic surgery; cardiopulmonary bypass

CARDIAC surgery is associated with marked alterations in global cardiovascular dynamics (eg, in blood pressure or cardiac output) and severely altered tissue perfusion as a result of transition to nonpulsatile blood flow during cardiopulmonary bypass (CPB). These macrocirculatory alterations potentially can result in tissue hypoperfusion, which is associated with tissue hypoxia.[1] Thus, it is one of the main goals for anesthesiologists to prevent or treat alterations in global cardiovascular dynamics with adequate hemodynamic management during cardiac surgery. Nonetheless, the ultimate goal of hemodynamic management during cardiac surgery is a sufficient supply of oxygen to the organs and tissue and to preserve microcirculatory perfusion.[2] As anesthesiologists, we hope to optimize the microcirculation by optimizing the macrocirculation.

The microcirculation is a complex network of microvessels, including arterioles, capillaries, and venules. Microcirculatory perfusion can be severely impaired during cardiac surgery, with or without CPB, as a result of reduced cardiac output,

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https://doi.org/10.1053/j.jvca.2019.10.038
1053-0770/

nonpulsatile blood flow, inflammation, hemodilution, and hypothermia.[3] In clinical practice, detection of these microcirculatory alterations can be challenging because microcirculatory alterations also may occur regionally or even when global hemodynamics are preserved. This may result in the so-called loss of hemodynamic coherence (or decoupling of the macrocirculation and microcirculation).[4]

The use of handheld vital microscopes (HVMs) enables direct visualization of the sublingual capillary bed and HVMs can be used to monitor microcirculatory perfusion.[5] Even though HVMs cannot directly measure tissue oxygenation yet, they allow for quantification of microcirculatory perfusion and convective and diffusive transport of oxygen. This application of HVMs has created a better understanding of microcirculatory alterations during cardiac surgery. However, their use in daily clinical routine outside of research applications still is not recommended.[5,6]

In this narrative review, the current knowledge is summarized and potential future directions regarding the monitoring of the sublingual microcirculation during cardiac surgery are discussed. Specifically, bedside monitoring of the microcirculation is the main focus, and how it may be used to guide therapeutic interventions in cardiac surgery patients is evaluated critically.

Methods to Assess Sublingual Microcirculation

The present review focuses on the use of HVMs to visualize and quantify microcirculatory perfusion. Other markers of microcirculatory perfusion and tissue oxygenation, such as the venous-arterial carbon dioxide tension difference,[7] central venous oxygen saturation,[8] or clinical assessments[9] (eg, the capillary refill time or the mottling score), are well-established in clinical practice but are beyond the scope of this review.

Handheld Vital Microscopes

HVMs allow for the noninvasive direct visualization of the capillary bed and recording of capillary perfusion. The first generation of these penlike probes was introduced in the late 1990s using orthogonal polarization spectral (OPS) imaging to visualize the capillary bed.[10] The microcirculation can be captured by placing the device on mucous membranes (eg, the sublingual or intestinal mucosa) or directly on an organ surface under sterile conditions. OPS imaging uses linearly polarized light that is reflected from the tissue surface and creates an image only from the scattered photons. Because of technological advancements, OPS has been replaced by sidestream dark field (SDF) imaging[11] and, more recently, incident dark field imaging.[12] Both technologies function with light-emitting diodes with a wavelength of 530 nm, the isosbestic point of hemoglobin absorption spectra, that are placed at the tip of the probes. Based on the light absorption of hemoglobin, the created image shows red blood cells as dark moving globules, whereas the surrounding tissue is displayed as a bright blur (Fig 1). Consequently, vessels must contain red blood cells in order to be visualized.[13]

SDF devices are connected to analog video cameras and a monitor for direct display. The devices require manual adjustment of illumination and image focus. Before an offline analysis is possible, the videos need to be converted into a digital signal. In comparison, incident dark field imaging uses a digital sensor that is synchronized to short-pulsed illumination resulting in sharper and higher contrast images with a larger field of view.[13]

The most commonly investigated regional site for HVMs is the sublingual mucosa because it is easily accessible and measurements are possible in both awake and sedated patients.[5] Even though measurements directly on organ surfaces have been proposed to describe the microcirculation of, for example, the liver,[14] the brain,[15] or the lung,[16] these measurements are rarely possible outside of the operating room. The sublingual microcirculation correlates well with the gastrointestinal[17] and renal perfusion[18] and therefore may be a useful surrogate for the microcirculation of vital organs. An updated expert consensus was published recently as a guideline for acquisition and interpretation of sublingual microcirculatory measurements.[5] These guidelines also include a series of standardized variables to describe the microcirculatory function.

Convective capacities of the microcirculation, such as red blood cell velocity, can be quantified using the microvascular flow index (MFI). The MFI is a semiquantitative assessment

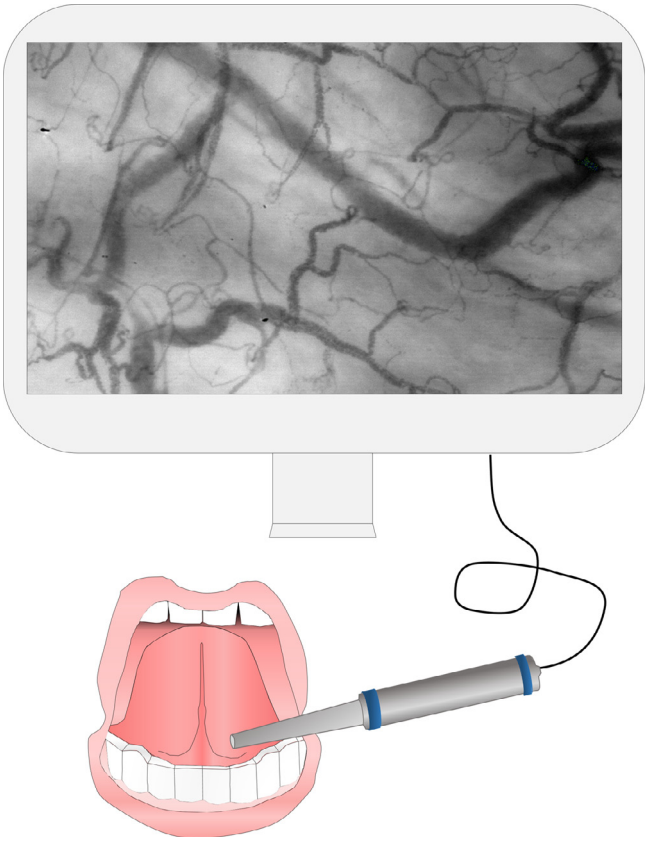

Fig 1. Visualization of the sublingual microcirculation using handheld vital microscopes. Video acquisition of the sublingual mucosa using a handheld vital microscope. Images are obtained with a handheld probe connected to a computer with video recording software.

of red blood cell velocity per image quadrant or an average of individual vessel flow. In addition, the proportion of perfused vessels (PPV), defined as a binominal determinant of perfusion ("flow" or "no flow"), can provide information on convective characteristics of the microcirculatory perfusion. More recently, a space-time diagram was proposed to directly determine single-cell red blood cell velocity in each vessel.

Diffusive capacities can be quantified by the total vessel density (TVD), defined as the sum of all capillaries containing red blood cells divided by the field of view. Likewise, the grid-based De Backer score can be used to approximate the TVD. The perfused vessel density (PVD) is an estimate for the functional capillary density (FCD) and reflects convective and diffusive components. The PVD only includes vessels with blood flow and is calculated as PPV multiplied by the TVD. The PVD can be considered the gold standard for experimental research, but absolute PVD measurements may vary by up to 30% because of methodical differences and observer dependence.[19] Recently, the FCD, which is based on automated analysis of blood cell flow in each individual vessel using the space-time diagram was proposed as a less subjective variable.[20] An overview of the most common microcirculatory variables is presented in Table 1.

Table 1
Microvascular Variables

Variable	Unit	Definition
MFI	au	Grid-based score: 0 = no flow, 1 = intermittent flow, 2 = sluggish flow, 3 = normal flow
PPV	%	Perfused vessels per total vessels based on binominal determinant of perfusion ("flow" or "no flow")
TVD	mm/mm^2	Total vessel area per surface area; surrogate for capillary distance
PVD	mm/mm^2	Percentage of perfused vessels × TVD; surrogate for diffusive and convective forces
FCD	mm/mm^2	Measure of PVD based on individual vessel STD
HI	au	Variable for flow heterogeneity
De Backer Score	n/mm	Surrogate for TVD
STD	mm/s	Automated analysis of red blood cell velocity

Abbreviations: au, arbitrary unit; FCD, functional capillary density; HI, heterogeneity index; MFI, microvascular flow index; PPV, proportion of perfused vessels; PVD, perfused vessel density; STD, space-time diagram; TVD, total vessel density.

An advantage of HVMs is that they enable multiple vessels to be visualized at the same time. This allows for the identification of blood flow variation within a single area of interest, referred to as flow heterogeneity. Determination of flow heterogeneity can help differentiate among different types of shock (eg, distributive versus cardiogenic shock). The heterogeneity index can be calculated based on the variation of MFI or PPV within the field of view. Although this is technically challenging, the heterogeneity index should be calculated based on red blood cell velocity variation of all analyzed vessels. Flow heterogeneity should not be confused with general heterogeneity of the sublingual microcirculatory anatomy. Even though single spot measurements may be performed to evaluate flow changes within a single vessel over time, it is consequently recommended to average measurements from at least 3 different sites to evaluate microcirculatory flow at a given time point.

The quality of videos recorded with an HVM needs to be checked before analysis, ideally by an independent observer. A quality score to evaluate brightness, focus, stability, duration, content, and pressure has been described to set quality standards for the video acquisition.[21]

Pressure artifacts caused by unnecessary force with the probe on the mucosa can restrict microcirculatory flow, leading to inaccurate measurements. Therefore, it is recommended that users of HVMs undergo theoretical and practical training.

The current reference method to convert HVM video sequences into quantitative measurements is a semiautomated analysis. A computer software preprocesses the video by improving brightness, enhancement of contrast, and background subtraction. The videos then are stabilized and the software automatically detects the vessels. The blood flow in each vessel is scored on a scale from 0 (no flow) to 3 (normal flow). Afterwards, all described variables can be calculated from these data. The automated vessel detection remains challenging and needs to be revised manually, leading to a hybrid of automatic and manual analyses.[13] The analysis of a single video can require up to 20 minutes, performed by an experienced operator.[20,22] This complex and time-consuming process is yet a major limitation.[23] Recently, an algorithm was proposed for fully automated video analysis, which can provide instant results and prevents observer bias during the analysis.[20]

Overall, the standardization of variables to describe the sublingual microcirculation is an important step toward bedside monitoring. However, the measurements are dependent on the investigator and the technology and analysis method used. Hence, it remains difficult to define normal values for the sublingual microcirculation and to compare results from different investigators.

Assessment of the Endothelial Glycocalyx and the Perfused Boundary Region

In the last years, the use of HVMs was suggested as a method to determine the integrity of the glycocalyx, the inner surface layer of the endothelium, through assessment of the perfused boundary region (PBR) (Fig 2).[24,25] The glycocalyx, which by itself is invisible to HVMs, covers the inner surface of microvascular endothelial cells and consists of a carbohydrate-rich structure. It plays an important role in vascular function and regulates fluid homeostasis as a key component of the ionic and colloid osmotic gradient. Under physiological conditions, there is a constant balance between synthesis and shear-induced degradation of the glycocalyx. Uncontrolled glycocalyx shedding can be caused by inflammation, ischemia/reperfusion injury, or acute volume loading (eg, during cardiac surgery).[26,27] Excessive glycocalyx shedding is associated with an impaired endothelial function, leading to increased vascular permeability and inadequate microcirculatory flow (see Fig 2).[28]

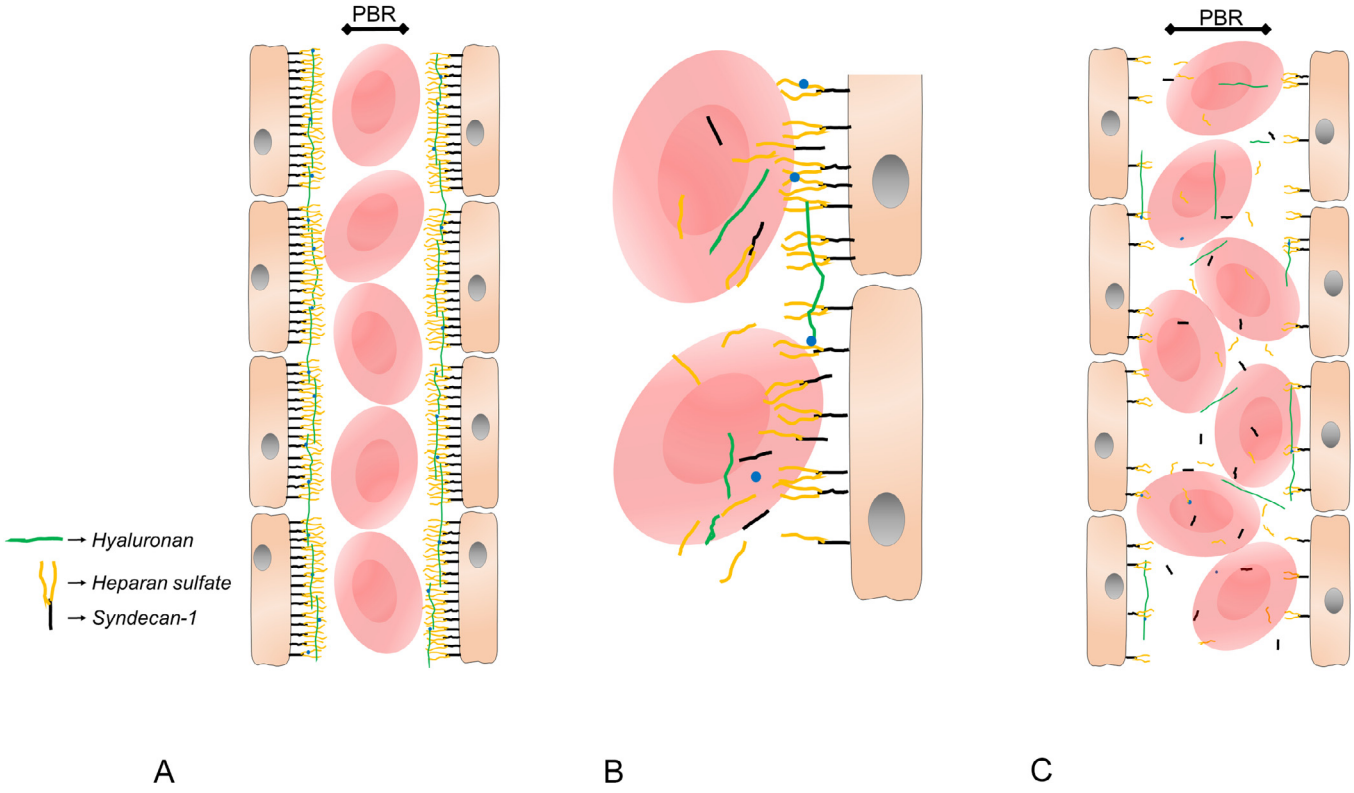

Fig 2. Microcirculatory perfusion. (A) Microcirculatory perfusion under normal conditions with intact glycocalyx layer. (B) Shedding of the glycocalyx layer due inflammation, flow alterations, medications, or excessive fluid administration. (C) Damaged endothelial glycocalyx layer with increased flow resistance and impaired microcirculatory perfusion. PBR, perfused boundary region.

The degraded structural components of the glycocalyx are released into the bloodstream and can be used as markers of endothelial damage. Plasma syndecan-1 and heparan sulfate are markers of glycocalyx degradation, which can be detected by enzyme-linked immunosorbent assay.[29] Because of the wide variation between absolute measurements, these markers are commonly solely recommended as trending variables. Limitations include their inability to detect restoration of the glycocalyx or to identify the cause of glycocalyx shedding.

HVMs also may be used to indirectly evaluate the integrity of the glycocalyx.[25] Under physiological conditions, red blood cells flow in the center region of the microvessels and do not breach the glycocalyx layer. When the glycocalyx is damaged or reduced, red blood cell flow deviates from the center of the vessel. Under these conditions, red blood cells may approach the endothelium and penetrate the glycocalyx.[24] This difference in flow deviation can be calculated as the difference between median and outer deviation of red blood cell flow in video sequences (see Fig 2). It is referred to as the PBR and functions as an indirect inverse measure for the glycocalyx dimensions.[30] This measurement requires an investigator who is well-experienced in the use of HVMs.

Clinical Application of Microcirculatory Monitoring During Cardiac Surgery

CPB leads to distinct cardiovascular changes, including hemodilution, nonpulsatile blood flow, and hypotension, which impair microcirculatory perfusion.[31] Until now, many studies that investigated the microcirculation during cardiac surgery were solely observational. In addition, most studies only included a small number of patients and had few measurement points as a result of the complex and time-consuming analysis. The heterogeneity in available data makes a direct comparison of the studies difficult. Only recently, standards for the assessment of sublingual microcirculation have been established.[5]

Overall, the available data indicate that cardiac surgery is associated with distinct microcirculatory alterations, especially during CPB. Several observational studies have shown that the PVD is reduced after the initiation of CPB. In addition, the MFI decreases throughout the intraoperative period, and CPB seems to be associated with an increase in flow heterogeneity.

One of the first prospective observational studies investigating the sublingual microcirculation during cardiac surgery with CPB used OPS imaging in 47 patients undergoing coronary artery bypass grafting (CABG), valve surgery, or a combination of both.[32] The results showed a decrease of the FCD (ie, PVD) during CPB, but values returned to baseline within 1 hour after termination of CPB. The decrease in PVD during CPB correlated with decreased esophageal temperature and hemoglobin levels, suggesting a detrimental effect on the sublingual microcirculation. Despite the recovery of the sublingual microcirculatory flow and systemic hemodynamics shortly after discontinuation of CPB, lactate levels increased further after termination of CPB. In another observational study including 22 patients undergoing valve surgery or on-pump CABG (ONCAB) (n = 9) or off-pump

CABG (OPCAB) (n = 6) or thyroidectomy (n = 7)[33], the CPB-induced reduction of PVD did not recover at the end of surgery despite recovery of mean arterial pressure (MAP) and cardiac output. All microcirculatory variables, except PPV, returned to baseline within 24 hours after surgery, and this could indicate a transient loss of macrocirculation-microcirculation coupling. Increases in lactate levels showed a correlation with the PVD in a linear regression analysis in that study.

The MFI was investigated with SDF imaging in a study including 25 patients undergoing ONCAB surgery, with 5 patients undergoing an additional valve procedure.[34] The results showed a decrease of the MFI after the initiation of CPB compared with values obtained after induction of anesthesia. In contrast to other findings, this trend was only observed in vessels between 25 and 50 μm diameter, whereas the MFI in small vessels (<25 μm) remained stable during CPB. Furthermore, MFI returned to baseline values after intensive care unit (ICU) admission. The PVD and PPV were not analyzed in this study.

Despite their heterogeneity in design, these studies suggest that cardiac surgery with CPB is associated with microcirculatory alterations during the intraoperative period. The observed decrease of PVD and MFI during CPB indicates reduced microcirculatory perfusion. Even though impaired microcirculatory perfusion during CPB could be explained by changes in macrocirculatory hemodynamics, such as cardiac output, postoperative recovery of macrocirculatory variables does not ensure the recovery of the microcirculation caused by a possible transient loss of macrocirculation-microcirculation coupling.

Endothelial Function and the Glycocalyx During Cardiac Surgery

The impairment of the glycocalyx is associated with reduced sublingual microcirculatory perfusion.[35] Recently, endothelial impairment and a simultaneous reduction of sublingual microcirculatory perfusion was observed in a number of studies.[25,28,35]

An observational study with 36 patients who underwent CABG surgery without CPB (n = 12), with pulsatile CPB (n = 12), and with nonpulsatile CPB (n = 12)[25] investigated the changes in microcirculatory perfusion and endothelial function. In line with previous studies, the PVD decreased in both groups during CPB. In addition, the PBR increased during the CPB phase, suggesting damage of the microvascular endothelium and its glycocalyx layer. Interestingly, microcirculatory perfusion returned to baseline values in the group with pulsatile CPB, whereas alterations persisted in the group with nonpulsatile CPB. Pearson correlation showed a correlation between PVD and PBR, indicating an inverse relationship between microcirculatory perfusion and the PBR. In patients who underwent OPCAB surgery, no changes in the PVD or the PBR, as markers of endothelial damage, were observed.

Another study with 15 patients showed a temporary decrease of PVD and the De Backer score during ONCAB and elective valve surgery.[36] The transient decrease of microcirculatory perfusion was associated with a simultaneous increase in glycocalyx shedding markers during anesthesia and CPB.

With increasing interest in the postoperative period, another study observed the sublingual microcirculation until 72 hours post-surgery in 17 ONCAB patients.[28] The results showed a persistent decrease of the PVD and PPV after the initiation of CPB until the last measurement at 72 hours post-surgery. Furthermore, CPB resulted in a trend of increased PBR and increased plasma syndecan-1 and heparan sulfate levels as signs of endothelial impairment.

These results provide evidence that an impaired sublingual microcirculation is associated with decreased glycocalyx dimensions that persist after cardiac surgery with CPB. Persistent damage to the endothelium could be an underlying mechanism for the loss of hemodynamic coherence and facilitate organ dysfunction. However, no outcomes were reported in these small cohorts. In addition, the macrohemodynamic data were not reported in these studies, and it can only be assumed that they were stable after the end of surgery.

On-Pump Versus Off-Pump Cardiac Surgery

CPB is an invasive procedure resulting in several unphysiological changes in the body. Hypothermia, hemodilution, and CPB-induced inflammation have been suggested as causes of microcirculatory impairment during CABG surgery. Unphysiological nonpulsatile blood flow and leukocyte and platelet activation during CPB facilitate inflammatory reactions and potentially harm the patient.[37] Therefore, several studies have addressed whether OPCAB surgery results in smaller microcirculatory alterations compared with ONCAB surgery.

Distinct differences in microcirculatory perfusion between ONCAB and OPCAB were investigated in a prospective observational study with 26 patients undergoing ONCAB (n = 13) or OPCAB (n = 13) surgery.[38] A reduction in microcirculatory perfusion was only found in the ONCAB group. As previously described, the initiation of CPB resulted in a decrease of the TVD and PVD. Furthermore, the MFI was reduced and microvascular impairment persisted after termination of CPB until ICU admission. No changes in microcirculatory perfusion were found in the OPCAB group.

Flow heterogeneity and tissue oxygenation, as determined by mixed venous oxygen saturation, were compared between ONCAB (n = 18) and OPCAB (n = 13) surgery in a study including 31 patients.[39] As expected, the heterogeneity index increased after the initiation of CPB with a simultaneous decrease in oxygen extraction and arteriovenous oxygen difference, suggesting reduced tissue oxygenation as a sign of possible microvascular shunting. Again, no relevant changes were observed in the OPCAB group. There were no marked alterations in microvascular flow or oxygenation markers in OPCAB patients during the study period.

Interestingly, in another observational study, neither ONCAB (n = 16) nor OPCAB (n = 16) surgery resulted in distinct sublingual microcirculatory alterations in 32 patients.[40] A total of 8 measurements of the sublingual microcirculation were performed in the perioperative period, including 5 intraoperative measurements. Despite a marked reduction in macrohemodynamic variables during CPB, only minor changes in

sublingual microcirculatory flow were observed. In addition, the results indicated a correlation of hypothermia and impaired sublingual microcirculation. However, only one video was obtained at each time point, which is considered insufficient according to current guidelines.[5]

An observational study including 48 patients undergoing either ONCAB (n = 24) or OPCAB (n = 24) surgery investigated sublingual microcirculation and sublingual oxygen saturation.[41] Measurements were performed with either an HVM using SDF imaging to determine sublingual perfusion (n = 24) or reflectance spectrophotometry to assess sublingual oxygen saturation (n = 24) resulting in 4 groups with 12 patients each. The results showed a decrease of PVD after the initiation of CPB. In addition, the sublingual venous flow velocity and oxygen saturation were increased during CPB in these patients, which suggests decreased oxygen extraction. The measurements in the OPCAB group were performed before and during cardiac luxation and showed that cardiac luxation resulted in a merely small decrease of the PVD, blood flow velocity, and sublingual oxygen saturation.

Distinct effects of cardiac luxation on microcirculatory perfusion also were investigated in a prospective observational study with 36 patients undergoing OPCAB surgery.[42] Microcirculatory perfusion was assessed either by sublingual measurement using SDF imaging (n = 12), sublingual oxygen saturation using reflectance spectrophotometry (n = 12), or cerebral oxygen saturation using near-infrared spectrophotometry (n = 12) before, during, and after cardiac luxation. In line with previous findings,[41] the analysis of sublingual capillary density showed no difference during the study period. In contrast, the blood cell velocity, sublingual oxygen saturation, and the cerebral oxygen saturation were reduced temporarily during cardiac luxation in the respective group. Nonetheless, the results from each group suggest a concurrent decrease in blood cell velocity, decreased sublingual microcirculatory perfusion, and decreased cerebral oxygen saturation.

In summary, several studies have shown that sublingual microcirculatory perfusion remains stable during OPCAB. However, OPCAB surgery often requires cardiac luxation for a posterior or anterolateral graft, resulting in abrupt decreases in cardiac output and MAP that also may affect microcirculatory perfusion.

Pulsatile Versus Nonpulsatile Flow During Cardiopulmonary Bypass

Because CPB is inevitable during some procedures, there is ongoing debate whether using pulsatile CPB flow may limit microcirculatory alterations compared with nonpulsatile CPB flow. Several observational studies have addressed this question.[43,44]

In a small randomized cohort study including 20 high-risk cardiac surgery patients, OPS imaging was used to investigate differences in sublingual microcirculation between pulsatile (n = 10) and nonpulsatile (n = 10) CPB.[45] Overall, the results showed a decrease in PVD during CPB in both groups. Furthermore, the reduction of the PVD was more severe in the nonpulsatile CPB group and persisted after surgery. In addition, the reduced PVD in the nonpulsatile CPB group was associated with an increased flow heterogeneity. In the group with pulsatile CPB, the values after surgery were comparable with baseline, indicating a rapid recovery of microcirculatory flow.

In a similar randomized study conducted by the same group, additional near-infrared spectroscopy measurements with repeated vascular occlusion tests were performed in 20 patients undergoing cardiac surgery with pulsatile (n = 10) or nonpulsatile (n = 10) CPB.[26] As shown in their previous study, the PVD was markedly reduced after the initiation of nonpulsatile CPB and during the first 24 hours after surgery. PVD reduction in the group with pulsatile CPB was smaller and recovered within the study period. Other assessed variables of vascular reactivity and regional oxygen saturation showed no substantial differences between the groups. The reperfusion slope after vascular occlusion was steeper in the pulsatile CPB group 24 hours after surgery, indicating that microcirculatory recruitment was better in the pulsatile CPB group. The differences in sublingual microcirculatory flow between pulsatile (n = 16) and nonpulsatile (n = 17) CPB also were investigated in a randomized cohort study with 33 patients undergoing ONCAB surgery.[46] Additional oxygenation markers were obtained at the start and end of aortic cross-clamping. The results showed temporary reductions of the PVD and MFI in the pulsatile CPB group whereas nonpulsatile CPB lead to a persistent decrease of the PVD and MFI. Postoperative MFI and PVD also were significantly lower in the nonpulsatile CPB group compared with the pulsatile CPB group. The results also showed higher oxygen consumption and a higher oxygen extraction rate at the end of aortic cross-clamping in the pulsatile CPB group.

Contrary results were reported in a randomized crossover study with 16 patients undergoing ONCAB or aortic valve replacement surgery.[47] Measurements of sublingual microcirculation were obtained 10 minutes after the initiation of CPB with pulsatile (n = 8) or nonpulsatile (n = 8) flow. After another 10 minutes the flow was switched to nonpulsatile or pulsatile, respectively. The results showed no differences in sublingual microcirculatory variables between the 2 flow forms, at least at this short time interval.

Furthermore, the results of an observational study with 20 patients undergoing standard CPB (n = 10) or miniaturized extracorporeal circulation (n = 10) indicate that miniaturized CPB might be a less harmful alternative to conventional CPB.[48] The miniaturized CPB resulted in minor microcirculatory alterations, and the decrease in PVD was significantly higher during conventional CPB. The MFI remained stable throughout the study period in both groups. These results indicate a beneficial effect of miniaturized CPB on microcirculatory perfusion. Even though it is a promising idea to prevent microcirculatory impairment with a less traumatic surgical procedure, these strategies are not applicable in all patients and procedures.

Overall, the available data from observational studies show that microcirculatory alterations commonly occur during cardiac surgery with CPB. These alterations include a decrease of the PVD and the MFI with a simultaneous increase of flow heterogeneity, which begin to manifest shortly after the initiation of CPB.

Several studies have shown that pulsatile flow thus has a smaller negative effect on microcirculatory perfusion than nonpulsatile flow during CPB. In addition, the use of miniaturized CPB systems seem to induce smaller microcirculatory alterations. Even though some studies show recovery of the sublingual microcirculation at the end of surgery, serum lactate, a surrogate marker of hypoperfusion, increased throughout the perioperative period in several studies. Furthermore, global hemodynamics are commonly restored at the end of surgery, which could indicate a loss of hemodynamic coherence. Therefore, it is unclear whether microcirculatory alterations are transient or persist into the postoperative period. With recent investigations on glycocalyx shedding, there is growing evidence that microcirculatory impairment does persist postoperatively.

Postoperative measurements of the sublingual microcirculation were performed in a recent pilot study with 10 post-cardiac surgery patients. The authors investigated the alterations of the sublingual microcirculation during the fluid de-escalation phase, describing reduction of excess fluids after surgery, with measurements 24 and 48 hours after discharge from the ICU.[49] The PVD and TVD increased during the de-escalation phase while patients received diuretic therapy (furosemide and/or spironolactone). This indicates improvement of the microcirculation during this period. The results suggest that HVM use is feasible in the postoperative phase and may be a useful tool to assess the patient's fluid status beyond the intraoperative period.[50] Given the lack of studies in this area, there are no clear implications on how monitoring the sublingual microcirculation could affect fluid management.

Interventions to Improve the Microcirculation During Cardiac Surgery

With an increasing understanding of microcirculatory alterations, therapeutic strategies have been proposed to improve microcirculatory flow during cardiac surgery.

The effects of the vasopressor phenylephrine on the sublingual microcirculation were investigated in an observational study with 15 patients undergoing ONCAB surgery.[51] Sublingual microcirculation was assessed with SDF imaging. Measurements were obtained after induction of anesthesia, after the initiation of CPB, during phenylephrine infusion, and after discontinuation of phenylephrine. In contrast to other studies, the MFI was not decreased after the initiation of CPB in this cohort. Subsequently, the α1-adrenoceptor agonist phenylephrine was administered at a mean rate of 1.4 μg/kg/min, increasing the perfusion pressure from 47 to 68 mmHg. Nevertheless, the infusion of phenylephrine during CPB resulted in a decrease of MFI and a simultaneous increase in sublingual oxygen saturation, indicating decreased oxygen extraction. The effects were reversed after discontinuation of phenylephrine infusion. The PPV and PVD were not reported in this study.

In a substudy of a large randomized clinical trial,[52] differences in sublingual microcirculatory flow were investigated in 36 patients randomly assigned to a low (40-50 mmHg) or high (70-80 mmHg) MAP undergoing ONCAB surgery.[53] In the high MAP group, a higher MAP was maintained through administration of higher doses of norepinephrine and repeated bolus injections of phenylephrine. However, there were no differences in any of the microcirculatory variables between the high and low MAP groups.

The effects of fluids were investigated in a study with 20 patients receiving either Ringer's lactate (n = 10) or hydroxyethyl starch (130/0.4) (n = 10) as priming solution during ONCAB surgery.[54] The sublingual microcirculation measurements were obtained before CPB, during CPB, at the end of surgery, and after 24 hours in the ICU. In both groups, the initiation of CPB was associated with a decrease of TVD and PVD without changes in the PPV. Only in the hydroxyethyl starch group did microcirculatory variables return to baseline at the end of surgery, whereas microcirculatory alterations persisted until 24 hours postoperatively in the Ringer's lactate group.

The role of different sedatives was studied in a prospective randomized blinded study in which 70 patients received either propofol infusion (n = 35) or propofol plus dexmedetomidine (n = 35) during ONCAB surgery with a target bispectral index of 40 to 60.[55] Dexmedetomidine is an α2-adrenoceptor agonist used for sedation and has been shown to reduce the inflammatory response to CPB.[56] The sublingual microcirculation was assessed before, during, and after CPB. The TVD was greater in the dexmedetomidine group throughout the whole study period. In contrast to other studies, the TVD, PVD, and PPV remained stable after the initiation of CPB in both groups. However, the MFI decreased in both groups after the initiation of CPB. After weaning from CPB, the TVD showed a slight decrease and the MFI returned to baseline values in the dexmedetomidine group, whereas other microcirculatory variables (PPV and PVD) remained unchanged. In the propofol only group, the MFI, PVD, and TVD decreased after termination of CPB and were significantly lower compared with those of the dexmedetomidine group for the last measurement. In line with other studies, the results indicated a deterioration of microvascular variables (MFI, PVD, and TVD) in patients undergoing cardiac surgery with CPB in the propofol only group. The additional infusion of dexmedetomidine resulted in no severe microcirculatory alterations and better perfusion compared with propofol only. Despite these differences in sublingual microcirculation, there were no differences in cardiac output, whereas lactate levels increased in both groups during the study period.

Overall, the discussed interventions still remain rather unspecific and additional research is necessary to find specific strategies to maintain microcirculatory blood flow.

Perspectives and Future Directions

HVMs have enabled a great leap in microcirculatory research and have created a better understanding of the underlying processes for hemodynamic alterations during and after cardiac surgery and in critically ill patients.[57] Although this method currently is still an experimental tool for the

Table 2
Summary of Presented Studies

First Author, Year	Number of Patients; Type of Surgery	Method; Variables	Measurement Time Points	Results
Bauer et al., 2007[32]	47 patients; ONCAB surgery, valve surgery with CPB, or combined valve and CABG surgery with CPB	OPS imaging; PVD, red blood cell velocity, microvascular diameter	After skin incision, after initiation of CPB, late phase of CPB, 1 h after discontinuation of CPB	Decrease in PVD in the late phase of CPB; weak correlation of microcirculation with hemoglobin concentration and esophageal temperature
De Backer et al., 2009[33]	22 patients; ONCAB, OPCAB, or thyroidectomy	OPS imaging; PVD, PPV, total vessel density (all sizes)	Before anesthesia, after anesthesia induction, during CPB, end of surgery, 6 and 24 h after surgery	Decrease in PVD and PPV in all groups after induction of anesthesia; further PVD and PPV decrease during CPB; smaller PVD decrease in OPCAB group compared with ONCAB group with recovery to baseline values after 24 h; correlation of microcirculatory alterations with peak lactate levels
den Uil et al., 2008[34]	25 patients; ONCAB (5 with additional valve procedure)	SDF imaging; MFI	Day before surgery, after anesthesia induction, during CPB, after admission to ICU, after body temperature recovery to 36.5˚C	Temporary decrease in MFI in medium sized microvessels during CPB with recovery at admission to ICU
Uz et al., 2018[49]	10 patients; post-cardiac surgery after discharge from ICU (fluid de-escalation phase)	IDF imaging; TVD, MFI, PPV, PVD (FCD)	shortly, 24 and 48 h after discharge from ICU	Increased TVD and PVD over the study period; no changes in MFI or PPV
Endothelial function and the glycocalyx during cardiac surgery				
Koning et al., 2016[25]	36 patients; ONCAB (pulsatile and nonpulsatile) and OPCAB surgery	SDF imaging; PVD, PBR	After anesthesia induction, during CPB/bypass grafting, at the end of surgery	Transient decrease in PVD and increase in PBR during pulsatile CPB; persistent decrease of PVD and increase in PBR during nonpulsatile CPB; inverse correlation of PBR with PVD; no microcirculatory changes in OPCAB group
Wu et al., 2019[36]	15 patients (in final analysis); ONCAB surgery, valve surgery with CPB, or combined valve and CABG surgery with CPB	SDF imaging; PVD, De Backer, syndecan-1, heparan sulfate, hyaluronan	Before anesthesia; after sternum splitting; after aortic clamping; before aortic de-clamping; 1, 4, 24, and 48 h after CPB	Transient decrease in PVD and De Backer score during CPB with recovery after 48 h; increase of syndecan-1, heparan sulfate, and hyaluronan during the early postoperative phase
Dekker et al., 2019[28]	17 patients; ONCAB surgery	SDF imaging; PVD, PPV, PBR; syndecan-1 and heparan sulfate levels	Day before surgery, after anesthesia induction, after initiation of CPB, red blood cell infusion after CPB, 24 and 72 h after surgery	Persistent decrease in PVD and PPV after the initiation of CPB until 72 h after surgery; increase of syndecan-1 and heparan sulfate after CPB; trend of increased PBR
On-pump v off-pump cardiac surgery				
Koning et al., 2014[38]	26 patients; ONCAB and OPCAB surgery	SDF imaging; MFI, TVD, PVD	After anesthesia induction, after aortic clamping, before aortic declamping (after first and second anastomoses in OPCAB group), after CPB, within 1 h after admission to ICU	Persistent decrease of PVD and PPV after initiation of CPB; decrease of MFI at the end of surgery in CBP group; no microcirculatory changes in OPCAB group

(*continued*)

Table 2 (*continued*)

First Author, Year	Number of Patients; Type of Surgery	Method; Variables	Measurement Time Points	Results
Koning et al., 2014[39]	31 patients; ONCAB and OPCAB surgery	SDF imaging; red blood cell velocity; heterogeneity index	After anesthesia induction, intraoperative (during CPB), within 1 h after admission to ICU	Increased microcirculatory flow heterogeneity after initiation of CPB with additional increase after admission to ICU in ONCAB group; no microcirculatory changes in OPCAB group
Bienz et al., 2016[40]	32 patients; ONCAB and OPCAB surgery	SDF imaging; small vessel count, vessel count with continuous flow, TVD, PVD, small vessel density	Before anesthesia, after anesthesia induction; graft 1, graft 2, graft 3, chest closure; 2 and 4 h after surgery	Unspecific minor microcirculatory alterations during ONCAB and OPCAB surgery
Atasaver et al., 2011[41]	48 patients; ONCAB and OPCAB surgery	SDF imaging; FCD, red blood cell velocity (capillary and venule), sublingual oxygen saturation	Before and after initiation of CPB (ONCAB), before and after cardiac luxation (OPCAB)	Decreased PVD after initiation of CPB with signs of decreased oxygen extraction; minor microcirculatory changes despite severe macrohemodynamic impairment during cardiac luxation
Atasaver et al., 201[42]	36 patients; OPCAB surgery	SDF imaging; FCD, red blood cell velocity, sublingual oxygen saturation, cerebral near-infrared spectrophotometry	Before and after cardiac luxation	Decreased red blood cell velocity, sublingual oxygen saturation, and cerebral oxygen index during cardiac positioning
Pulsatile versus nonpulsatile flow during CPB				
O'Neil et al., 2012[45]	20 patients; high-risk ONCAB surgery with concomitant procedure with pulsatile or nonpulsatile CPB	OPS imaging; PPV for each flow score (0-4)	After anesthesia induction; 30 min after initiation of CPB; 90 min after initiation of CPB; 1, 24, and 48 h after CPB	Decreased PPV in both groups, with more severe decrease in PPV and increased signs of heterogeneous flow in nonpulsatile CPB group; recovery to baseline values only in the pulsatile CPB group
O'Neil et al., 2018[26]	20 patients; high-risk ONCAB surgery with concomitant procedure with pulsatile or nonpulsatile CPB	OPS imaging; PPV separated for each flow score (0-3), vessel density, near-infrared spectroscopy, vascular occlusion test	After anesthesia induction, 30 min after initiation of CPB, 90 min after initiation of CPB, 1 and 24 h after CPB	Decreased PPV in both groups, with more severe decrease in PPV and increased signs of heterogeneous flow in nonpulsatile CPB group; recovery to baseline values only in the pulsatile CPB group; steeper reperfusion slope in the pulsatile CPB group
Koning et al., 2012[46]	33 patients; ONCAB surgery with pulsatile or nonpulsatile CPB	SDF imaging; TVD, PVD, MFI	After anesthesia induction, after initiation of CPB, after aortic clamping, before aortic declamping, after aortic declamping, end of surgery, within 1 h after surgery	Temporary decrease of PVD and MFI in pulsatile CPB group; persistent decrease of PVD and MFI in nonpulsatile CPB group
Elbers et al., 2011[47]	16 patients; ONCAB or aortic valve repair surgery with pulsatile and nonpulsatile CPB (crossover design)	SDF imaging; PVD, PPV, heterogeneity index, PVD, MFI	Once during pulsatile CPB and once during nonpulsatile CPB	No major differences in microvascular variables between pulsatile and nonpulsatile flow

(*continued*)

Table 2 (*continued*)

First Author, Year	Number of Patients; Type of Surgery	Method; Variables	Measurement Time Points	Results
Yuruk et al., 2012[48]	20 patients; ONCAB surgery with conventional or miniaturized CPB system	SDF imaging; PVD	Before, during, and after CPB	Minor microcirculatory alterations during miniaturized CPB; decrease of PVD during conventional CPB
Interventions to improve the microcirculation during cardiac surgery				
Maier et al., 2009[51]	15 patients; ONCAB surgery	SDF imaging; effect of phenylephrine, perfusion units, MFI, microcirculatory hemoglobin oxygen saturation	After anesthesia induction, after initiation of CPB, with phenylephrine infusion during CPB, after discontinuation of phenylephrine infusion during CPB	No decrease of MFI after onset of CPB, but decrease of MFI during phenylephrine infusion with parallel increase in microcirculatory hemoglobin oxygen saturation; both returned to baseline after discontinuation of phenylephrine infusion
Holmgaard et al., 2018[53]	36 patients; ONCAB surgery	SDF imaging; comparison of low MAP (40-50 mmHg) and high MAP (70-80 mmHg), MFI, TVD, PVD, PPV, heterogeneity index	After anesthesia induction, during CPB, at the end of surgery	No significant differences in microcirculatory variables between low and high MAP groups
Kılıçaslan et al., 2015[54]	20 patients; ONCAB surgery	SDF imaging; Ringer's lactate or HES (130/0.4) as priming solution, TVD, PVD, PPV, heterogeneity index	After anesthesia induction, before initiation of CPB, during CPB, at the end of surgery, 24 h after surgery	Decrease of TVD and PVD during CPB, which returned to baseline after surgery only in the HES group; no changes in PPV or heterogeneity index were observed
Mohamed et al., 2019[55]	70 patients; ONCAB surgery	SDF imaging; propofol or propofol plus dexmedetomidine, MFI, PVD, TVD	Before initiation of CPB, 30 min after initiation of CPB, 30 min after CPB	PVD and TVD remained unaltered after initiation of CPB, whereas MFI decreased in both groups; recovery of MFI in dexmedetomidine group after CPB; decrease in MFI, PVD, and PPV after CPB in propofol group

Abbreviations: CPB, cardiopulmonary bypass; HES, hydroxyethyl starch; ICU, intensive care unit; IDF, incident dark field; MAP, mean arterial pressure; MFI, microvascular flow index; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; OPS, orthogonal polarization spectral; PBR, perfused boundary region; PPV, proportion of perfused vessels; PVD, perfused vessel density; SDF, sidestream dark field; TVD, total vessel density.

assessment of microcirculatory flow, it may be considered for routine care by doctors and even nurses[58] in the future.

However, the effects of CPB; anesthesia, including fluid administration and vasoactive medication administration; and other medication on the microcirculation still require further investigation. Studies published on the microcirculation during cardiac surgery are very heterogenous with regard to investigated exposures and outcomes (Table 2). Most studies included only a very limited number of patients and vary widely in the analyzed microcirculatory variables. Therefore, the effect of microcirculatory alterations on perioperative complications and patient outcomes mainly remains unclear. The recently published consensus on assessment of the sublingual microcirculation may harmonize and improve the scientific methods in microcirculation research.[5] The time-consuming offline analysis of the video sequences obtained with HVMs is another crucial limitation that may be overcome in the near future. A recently published algorithm allows for automated measurement of TVD, FCD, and PPV, which might make the bedside use of HVMs possible.[20] The development of an automated real-time analysis of microcirculation videos may enable more widespread application of HVMs and possibly point-of-care use and bedside diagnosis of microcirculatory alterations.

However, there is an ongoing debate whether the routine application of microcirculatory monitoring can improve patient outcome.[23] Because microcirculatory monitoring (as any monitoring) by itself will not improve patient outcome, it is necessary to test whether a hemodynamic strategy (fluid administration, catecholamines, transfusion, and specific microcirculatory treatment) based on microcirculatory variables can improve postoperative outcomes.

As a first step to develop these treatment strategies, a basic understanding of how the microcirculation works is needed. Although there is evidence of microcirculatory changes during cardiac surgery, additional research using the latest generation of HVMs and automated analysis is necessary to paint a better picture. A second step is the identification of treatment targets and, possibly, target values for the respective microcirculatory variables. In the era of individualized and personalized medicine, it has to be questioned whether "normal" values are appropriate or necessary. "Normal" values might provide a false idea of healthy flow because each patient might have an individual flow profile. As recently suggested, a preoperative assessment of the cardiovascular status could be used to guide perioperative hemodynamic therapy.[59] Then, as a third step, routinely assessed microcirculatory variables could be integrated into protocolized personalized hemodynamic therapy algorithms.[60] If these steps are completed, cardiac surgery patients may be prone to benefit from the use of HVMs. Hemodynamic treatment guided by microcirculatory measurements might help to improve patient outcome by reducing perioperative complications (eg, acute kidney injury or stroke).

Conclusions

In recent years, research on the microcirculation has led to a better understanding of microcirculatory perfusion during cardiac surgery and consequences of microvascular alterations on perioperative complications and patient outcome.[61,62] The use of HVMs is a noninvasive method that is safe and feasible during cardiac surgery and that may be of value to improve and individualize hemodynamic management. However, the effects of perioperative interventions, including fluid administration, catecholamines, and other medication, on the microcirculation still require further investigation. Even though technical advancements will help to overcome some of the methodical limitations, therapeutic targets need to be identified to enable microcirculatory monitoring to be implemented in routine clinical practice rather than used only in experimental studies.

Conflict of Interest

J. Duranteau has received honoraria for giving lectures from Fresenius (Bad Homburg, Germany) and LFB (Les Ulis, France). T.W.L. Scheeren has received research grants and honoraria from Edwards Lifesciences (Irvine, CA) and Masimo Inc. (Irvine, CA) for consulting and lecturing and from Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing. B. Saugel collaborates with Pulsion Medical Systems SE as a member of the medical advisory board and has received institutional restricted research grants, honoraria for giving lectures, and refunds for travel expenses from Pulsion Medical Systems SE; has received research support, honoraria for giving lectures, and honoraria for consulting from Edwards Lifesciences; has received institutional restricted research grants, honoraria for giving lectures, and refunds for travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria); has received institutional restricted research grants, honoraria for consulting, and refunds for travel expenses from Tensys Medical Inc (San Diego, CA); has received institutional restricted research grants from Retia Medical LLC (Valhalla, NY); and has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany).

References

1 Gaudino M, Angelini GD, Antoniades C, et al. Off-pump coronary artery bypass grafting: 30 years of debate. J Am Heart Assoc 2018;7:e009934.
2 Ocak I, Kara A, Ince C. Monitoring microcirculation. Best Pract Res Clin Anaesthesiol 2016;30:407–18.
3 Haase-Fielitz A, Haase M, Bellomo R, et al. Perioperative hemodynamic instability and fluid overload are associated with increasing acute kidney injury severity and worse outcome after cardiac surgery. Blood Purif 2017;43:298–308.
4 Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care 2015;19(Suppl 3):S8.
5 Ince C, Boerma EC, Cecconi M, 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.
6 Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1795–815.
7 Habicher M, von Heymann C, Spies CD, et al. Central venous-arterial pCO2 difference identifies microcirculatory hypoperfusion in cardiac surgical patients with normal central venous oxygen saturation: A retrospective analysis. J Cardiothorac Vasc Anesth 2015;29:646–55.
8 Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184:514–20.
9 Huber W, Zanner R, Schneider G, et al. Assessment of regional perfusion and organ function: Less and non-invasive techniques. Front Med (Lausanne) 2019;6:50.
10 Groner W, Winkelman JW, Harris AG, et al. Orthogonal polarization spectral imaging: A new method for study of the microcirculation. Nat Med 1999;5:1209–12.
11 Goedhart PT, Khalilzada M, Bezemer R, et al. Sidestream Dark Field (SDF) imaging: A novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 2007;15:15101–14.
12 Aykut G, Veenstra G, Scorcella C, et al. Cytocam-IDF (incident dark field illumination) imaging for bedside monitoring of the microcirculation. Intensive Care Med Exp 2015;3:4.
13 Massey MJ, Shapiro NI. A guide to human in vivo microcirculatory flow image analysis. Crit Care 2016;20:35.
14 Nilsson J, Eriksson S, Blind PJ, et al. Microcirculation changes during liver resection—a clinical study. Microvasc Res 2014;94:47–51.
15 Perez-Barcena J, Goedhart P, Ibanez J, et al. Direct observation of human microcirculation during decompressive craniectomy after stroke. Crit Care Med 2011;39:1126–9.
16 den Uil CA, Bezemer R, Miranda DR, et al. Intra-operative assessment of human pulmonary alveoli in vivo using Sidestream Dark Field imaging: A feasibility study. Med Sci Monit 2009;15;MT137-141.
17 Verdant CL, De Backer D, Bruhn A, et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: A quantitative analysis. Crit Care Med 2009;37:2875–81.
18 Lima A, van Rooij T, Ergin B, et al. Dynamic contrast-enhanced ultrasound identifies microcirculatory alterations in sepsis-iduced acute kidney injury. Crit Care Med 2018;46:1284–92.
19 Vincent JL, Taccone FS. Microvascular monitoring - Do 'global' markers help? Best Pract Res Clin Anaesthesiol 2016;30:399–405.
20 Hilty MP, Guerci P, Ince Y, et al. MicroTools enables automated quantification of capillary density and red blood cell velocity in handheld vital microscopy. Commun Biol 2019;2:217.

21 Massey MJ, Larochelle E, Najarro G, et al. 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.
22 Hessler M, Arnemann PH, Zamit F, et al. A new complimentary web-based tool for manual analysis of microcirculation videos: Validation of the Capillary Mapper against the current gold standard AVA 3.2. Microcirculation 2018;25:e12505.
23 De Backer D. Is microcirculatory assessment ready for regular use in clinical practice? Curr Opin Crit Care 2019;25:280–4.
24 Boer C, Koning NJ, Van Teeffelen J, et al. Changes in microcirculatory perfusion during cardiac surgery are paralleled by alterations in glycocalyx integrity. Crit Care 2013;17(Suppl 2):P212.
25 Koning NJ, Vonk AB, Vink H, et al. Side-by-side alterations in glycocalyx thickness and perfused microvascular density during acute microcirculatory alterations in cardiac surgery. Microcirculation 2016;23:69–74.
26 O'Neil MP, Alie R, Guo LR, et al. Microvascular responsiveness to pulsatile and nonpulsatile flow during cardiopulmonary bypass. Ann Thorac Surg 2018;105:1745–53.
27 Pesonen E, Passov A, Andersson S, et al. Glycocalyx degradation and inflammation in cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:341–5.
28 Dekker NAM, Veerhoek D, Koning NJ, et al. Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. Anaesthesia 2019;74:609–18.
29 Myers GJ, Wegner J. Endothelial glycocalyx and cardiopulmonary bypass. J Extra Corpor Technol 2017;49:174–81.
30 Lee DH, Dane MJ, van den Berg BM, et al. Deeper penetration of erythrocytes into the endothelial glycocalyx is associated with impaired microvascular perfusion. PLoS One 2014;9:e96477.
31 Koning NJ, Atasever B, Vonk AB, et al. Changes in microcirculatory perfusion and oxygenation during cardiac surgery with or without cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2014;28:1331–40.
32 Bauer A, Kofler S, Thiel M, et al. Monitoring of the sublingual microcirculation in cardiac surgery using orthogonal polarization spectral imaging: Preliminary results. Anesthesiology 2007;107:939–45.
33 De Backer D, Dubois MJ, Schmartz D, et al. Microcirculatory alterations in cardiac surgery: Effects of cardiopulmonary bypass and anesthesia. Ann Thorac Surg 2009;88:1396–403.
34 den Uil CA, Lagrand WK, Spronk PE, et al. Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: A pilot study. J Thorac Cardiovasc Surg 2008;136:129–34.
35 Cabrales P, Vazquez BY, Tsai AG, et al. Microvascular and capillary perfusion following glycocalyx degradation. J Appl Physiol 2007;102(1985):2251–9.
36 Wu Q, Gao W, Zhou J, et al. Correlation between acute degradation of the endothelial glycocalyx and microcirculation dysfunction during cardiopulmonary bypass in cardiac surgery. Microvasc Res 2019;124:37–42.
37 Greilich PE, Brouse CF, Rinder HM, et al. Monocyte activation in on-pump versus off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth 2008;22:361–8.
38 Koning NJ, Vonk AB, Meesters MI, et al. Microcirculatory perfusion is preserved during off-pump but not on-pump cardiac surgery. J Cardiothorac Vasc Anesth 2014;28:336–41.
39 Koning NJ, Simon LE, Asfar P, et al. Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. Am J Physiol Heart Circ Physiol 2014;307:H967–75.
40 Bienz M, Drullinsky D, Stevens LM, et al. Microcirculatory response during on-pump versus off-pump coronary artery bypass graft surgery. Perfusion 2016;31:207–15.
41 Atasever B, Boer C, Goedhart P, et al. Distinct alterations in sublingual microcirculatory blood flow and hemoglobin oxygenation in on-pump and off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011;25:784–90.
42 Atasever B, Boer C, Speekenbrink R, et al. Cardiac displacement during off-pump coronary artery bypass grafting surgery: Effect on sublingual microcirculation and cerebral oxygenation. Interact Cardiovasc Thorac Surg 2011;13:573–7.
43 Alghamdi AA, Latter DA. Pulsatile versus nonpulsatile cardiopulmonary bypass flow: An evidence-based approach. J Card Surg 2006;21:347–54.
44 Hoefeijzers MP, ter Horst LH, Koning N, et al. The pulsatile perfusion debate in cardiac surgery: Answers from the microcirculation? J Cardiothorac Vasc Anesth 2015;29:761–7.
45 O'Neil MP, Fleming JC, Badhwar A, et al. Pulsatile versus nonpulsatile flow during cardiopulmonary bypass: Microcirculatory and systemic effects. Ann Thorac Surg 2012;94:2046–53.
46 Koning NJ, Vonk AB, van Barneveld LJ, et al. Pulsatile flow during cardiopulmonary bypass preserves postoperative microcirculatory perfusion irrespective of systemic hemodynamics. J Appl Physiol 2012;112(1985):1727–34.
47 Elbers PW, Wijbenga J, Solinger F, et al. Direct observation of the human microcirculation during cardiopulmonary bypass: Effects of pulsatile perfusion. J Cardiothorac Vasc Anesth 2011;25:250–5.
48 Yuruk K, Bezemer R, Euser M, et al. The effects of conventional extracorporeal circulation versus miniaturized extracorporeal circulation on microcirculation during cardiopulmonary bypass-assisted coronary artery bypass graft surgery. Interact Cardiovasc Thorac Surg 2012;15:364–70.
49 Uz Z, Ince C, Guerci P, et al. Recruitment of sublingual microcirculation using handheld incident dark field imaging as a routine measurement tool during the postoperative de-escalation phase-a pilot study in post ICU cardiac surgery patients. Perioper Med 2018;7:18.
50 Arnemann P, Seidel L, Ertmer C. Haemodynamic coherence - the relevance of fluid therapy. Best Pract Res Clin Anaesthesiol 2016;30:419–27.
51 Maier S, Hasibeder WR, Hengl C, et al. Effects of phenylephrine on the sublingual microcirculation during cardiopulmonary bypass. Br J Anaesth 2009;102:485–91.
52 Vedel AG, Holmgaard F, Rasmussen LS, et al. High-target versus low-target blood pressure management during cardiopulmonary bypass to prevent cerebral injury in cardiac surgery patients: A randomized controlled trial. Circulation 2018;137:1770–80.
53 Holmgaard F, Vedel AG, Ravn HB, et al. Impact of mean arterial pressure on sublingual microcirculation during cardiopulmonary bypass-secondary outcome from a randomized clinical trial. Microcirculation 2018;25:e12459.
54 Kılıçaslan B, Çelebioğlu B, Çil H, et al. The effects of hydroxyethyl starch (130/0.4) as the priming solution on microcirculation in coronary bypass grafting (CABG) surgery. J Cardiothorac Vasc Anesth 2015;29:S57.
55 Mohamed H, Hosny H, Tawadros Md P, et al. Effect of dexmedetomidine infusion on sublingual microcirculation in patients undergoing on-pump coronary artery bypass graft surgery: A prospective randomized trial. J Cardiothorac Vasc Anesth 2019;33:334–40.
56 Ueki M, Kawasaki T, Habe K, et al. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia 2014;69:693–700.
57 Kara A, Akin S, Ince C. The response of the microcirculation to cardiac surgery. Curr Opin Anaesthesiol 2016;29:85–93.
58 Tanaka S, Harrois A, Nicolai C, et al. Qualitative real-time analysis by nurses of sublingual microcirculation in intensive care unit: The MICRONURSE study. Crit Care 2015;19:388.
59 Saugel B, Reese PC, Sessler DI, et al. Automated ambulatory blood pressure measurements and intraoperative hypotension in patients having noncardiac surgery with general anesthesia: A prospective observational study. Anesthesiology 2019;131:74–83.
60 Saugel B, Vincent JL. Protocolised personalised peri-operative haemodynamic management. Eur J Anaesthesiol 2019;36:551–4.
61 den Uil CA, Lagrand WK, van der Ent M, et al. Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. Eur Heart J 2010;31:3032–9.
62 De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: Impact of time of assessment and relationship with outcome. Crit Care Med 2013;41:791–9.