Applied Cardiopulmonary Pathophysiology 16: 229-248, 2012

Sublingual microcirculation

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Abstract

Microcirculation plays a crucial role in the interaction between blood and tissue both in physiological and pathophysiological states. Orthogonal polarization spectral (OPS) and Side stream dark field (SDF) imaging are relatively new noninvasive methods that allow the investigation of mucosal sites, especially sublingual area, particularly in critically ill patients. OPS imaging has been validated against conventional capillary microscopy, results demonstrated that OPS images provided similar values for RBC-velocity and capillary diameter as those measured by conventional capillary microscopy. Despite some limitations, sublingual microcirculation has been considered as a possible surrogate measure for splanchnic blood flow. There are several areas in human medicine, where observation of sublingual microcirculatory bed has been carried out – different kinds of shock, cardiac arrest, effect of various treatments, drugs and extreme physiological conditions as well. Early detection of microvascular abnormality seems to be a key factor to start early therapeutic intervention in order to reverse microvascular dysfunction, to maintain efficient microvascular flow and to contribute to better clinical outcome. In experimental setting, observing sublingual microcirculation is an important part of any research focused on the role of microcirculation during various diseases models and to assess effect of different treatment modalities on microcirculation.

Key words: Microcirculation, sublingual, Orthogonal polarization spectral imaging (OPS), Side stream dark field imaging (SDF)

Introduction

Microcirculation plays a crucial role in the interaction between blood and tissue both in physiological and pathophysiological states. Analysis of microvascular blood flow alterations gives a unique perspective to study processes at the microscopic level in clinical medicine (1). Despite the critical role of microcirculation in numerous diseases including diabetes, hypertension, sepsis or multiple organ failure (2-5), methods for direct visualization and quantitative assessment of the human microcirculation at the bedside are limited (6). The interest in microhemodynamic monitoring (7) grows with the understanding of microcirculatory pathology in its molecular level, especially in critically ill patients (5, 8, 9). The gold standard for assessment of microcirculation is intravital microscopy (IVM). However, this technique cannot be performed in humans because there is a need for fluorescent dyes and transillumination. The size of instrumentation for IVM can be also a limiting factor for its use in clinical medicine. For many years, capillary microscopy (capillaroscopy, nailfold videomicroscopy) has been the only method for assessment of the human microcirculation at the microscopic level in vivo. The use of this technique in humans is limited to easily accessible surfaces like the skin, nailfold,

lip or the bulbar conjunctiva (10). The nailfold microcirculation is extremely sensitive to external temperature and vasoconstrictive agents (11) and the nailfold videomicroscopy may not be a reliable indicator of microcirculation in other parts of the body, particularly in critically ill patients. Orthogonal polarization spectral (OPS) and Side stream dark field imaging (SDF) represent relatively new non-invasive methods that allow the investigation of mucosal sites, especially sublingual area. There is growing evidence that relationship between microcirculatory dysfunction and clinical outcome exists (12, 13). Nevertheless, this technique may be used in experimental settings as well. Access to sublingual area seems to be very easy, however the key question is whether this area represents microcirculation status of other body tissues or organs; nevertheless, sublingual area represents one of the best accessible mucosa surfaces in humans.

Anatomy

The sublingual area is one of the easiest to access areas in human mucosal surfaces. The major arteries supplying this area are the external carotid artery, the lingual artery and the sublingual artery (9, 14-16) (Figure 1). Only limited number of sublingual arterioles are present, whereas numerous capillaries (less than 20 um) and venules (20-100 um) are present in this area (9, 17, 18). External carotid artery contributes to the perfusion of sublingual mucosa and therefore sublingual perfusion may reflect cerebral blood flow as well (9). Despite this fact, only few studies focus on this relationship (19, 20). Sublingual microcirculation has been considered as a surrogate measure for splanchnic blood flow, mainly because 1) the tongue and related areas share a common embryogenic origin with the gut and 2) the close correlation between sublingual capnometry and gastric tonometry (21-24).

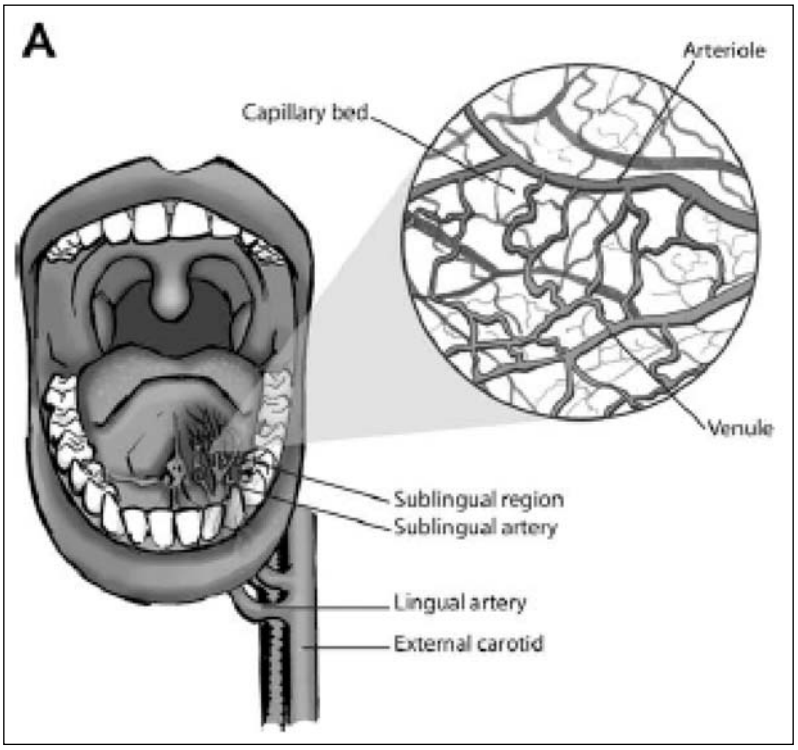

Figure 1: Anatomy of sublingual area (adapted from Klijn, 2008)

Imaging techniques

Orthogonal Polarization Spectral Imaging and Side Stream Dark Field Imaging

Orthogonal Polarization Spectral Imaging (OPS) technology was invented by Cytometrics, Inc. (Philadelphia, PA, USA) during the process of developing a videomicroscope able to create high contrast images of blood in the microcirculation using reflected light. The original purpose was to develop an instrument for analyzing images of the microcirculation using spectrophotometry in order to compute a complete blood count (CBC) without removing blood from the body (25,26).

In conventional reflectance imaging (CRI), high-quality image contrast and detail are limited by multiple surface scattering and turbidity of the surrounding tissue (25). In OPS imaging, the main difference from CRI consists in the phenomenon of cross-polarization that reduces these effects. As shown in schematic figure (Figure 2), incident light is linearly polarized in one plane and projected through a beam splitter onto the subject. Most of the reflected light keeps its polarization and cannot pass through the orthogonal polarizer (analyzer) to form the image. The light that penetrates the tissue more deeply and undergoes multiple scattering events becomes depolarized. There is evidence that more than ten scattering events are necessary to depolarize the light effectively (27, 28). Hence, only this depolarized scattered light passing through orthogonal polarizer (analyzer) effectively back-illuminates absorbing material in the foreground. A wavelength of the emitted light (548 nm) was chosen to achieve optimal imaging of the microcirculation because at this wavelength oxy- and deoxy-hemoglobin absorb the light equally. Thus, the blood vessels of the microcirculation can be visualized by OPS imaging. A detailed description of OPS imaging technology and further technical improvement has been published previously (26,29). A new device based on OPS technology has been developed – side stream dark field (SDF) imaging. In this modality a

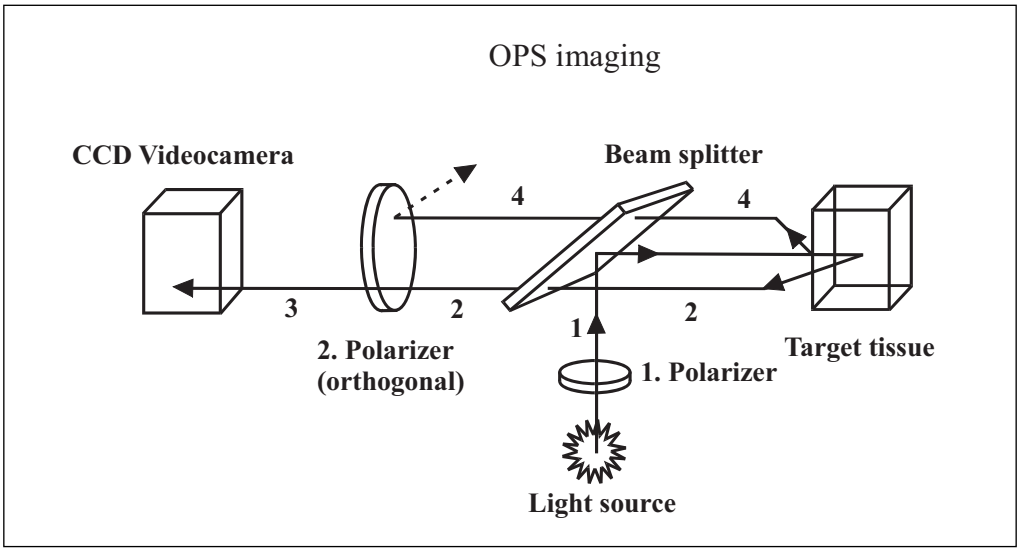

Figure 2: OPS imaging, optical scheme. (1) Incident polarized light is reflected toward the target tissue by beam splitter (2). Depolarized scattered light passes through orthogonal polarizer-analyzer and (3) it is projected onto CCD videocamera. (4) Reflected polarized light eliminated by orthogonal polarizer (adapted from Cerny, 2006)

light guide imaging the microcirculation is surrounded by light-emitting diodes of a wavelength (530 nm) absorbed by the hemoglobin of erythrocytes so that they can be clearly observed as flowing cells. Covered by a disposable cap the probe is placed on tissue surfaces. This way of observing the microcirculation provides clear images of the capillaries without blurring (Figure 3) (30, 31). Recent clinical studies of the human microcirculation using OPS imaging in various pathological states have shown a wide spectrum of different clinical applications with evident impact on diagnosis, treatment or prognosis assessment. Thus, there is a great effort to validate OPS imaging for various clinical purposes. The validation experimental studies are mostly based on comparison of IVM and OPS imaging where IVM is supposed to be a gold standard for main microcirculation parameters assessment (32-34). OPS imaging has been validated especially in animals (32,35,36) and partly in humans (37). Current knowledge on the microcircu-

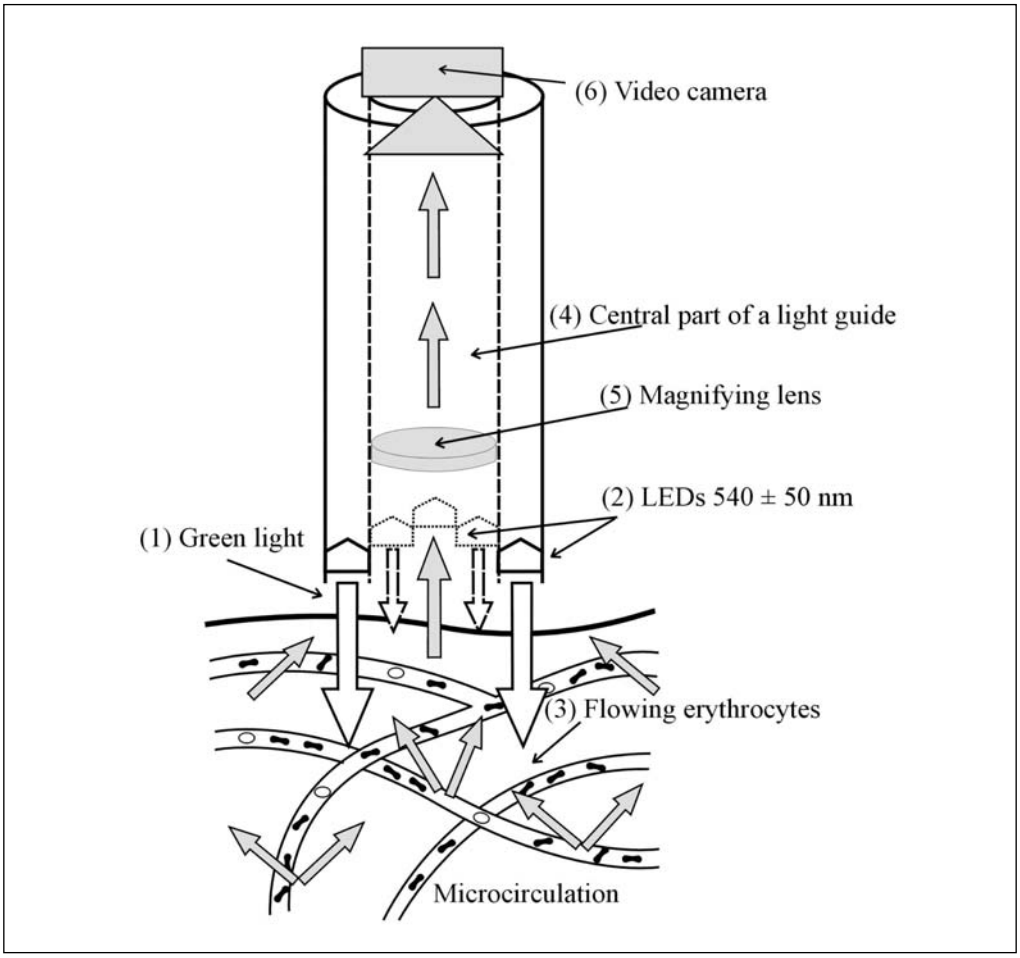

Figure 3: SDF imaging, optical scheme. (1) Green light is emitted by (2) peripheral 540 ± 50 nm light-emitting diodes (LEDs) toward tissue arranged in a circle at the end of the light guide. The microcirculation is directly penetrated and illuminated from the side by green light absorbed by hemoglobin of erythrocytes which are observed as (3) dark moving cells. Imaging central part of light guide (4) is optically isolated from LEDs. A magnifying lens (5) projects the image onto a camera (6) (adapted from Cerny et al, 2006)

lation is mainly derived from animal studies. Measurements of the microcirculation in humans were limited to easily accessible surfaces such as skin and nailfold capillaries. The basic validation studies in animals have been performed both on peripheral tissues and solid organs. OPS imaging techniques has been validated using a highly standardized model of the hamster dorsal skinfold chambre (38). Four main parameters were measured to validate CYTOSCAN™ A/R against standard fluorescent videomicroscopy under normal conditions and in ischemia/reperfusion injury: functional capillary density (FCD), arteriolar and venular diameter and venular red blood cell (RBC) velocity. There were not significant differences between the two techniques for any of the parameters using Bland-Altman analysis. Similar validation study in ischemia/reperfusion injury realized using the CYTOSCAN E-II has confirmed the comparability of OPS imaging and IVM (38). Functional capillary density is defined as the length of perfused capillaries per unit area and is given in cm/cm^2. The FCD is a parameter of the tissue perfusion and an indirect indicator of the oxygen delivery. It is widely used in clinical studies as semiquantitative method to determine capillary density and the proportion of perfused capillaries. OPS imaging was also validated against IVM in mouse skin flaps and cremaster muscle preparations. The velocities in straight vessels were comparable in both methods (39). The dorsal skinfold chamber model in hamsters was also used to validate OPS imaging under conditions of hemodilution with a wide range of hematocrit (Hct) (38). Bland-Altman analysis of the vessel diameter and FCD showed good agreement between OPS imaging technique and IVM at a wide range of Hct. OPS imaging has been validated against IVM on solid organs in rats, the model of ischemia/reperfusion injury of the rat liver has been used for the assessment of hepatic microcirculation applying both techniques (40). There was significant agreement for data obtained from both methods; correlation parameters for sinusoidal perfusion rate, vessel diameter and venular RBC velocity were significant. The pancreatic microcirculation has also been under investigation using OPS imaging and IVM (41). Absolute values of the pancreatic functional capillary density were not significantly different between the two methods. Bland-Altman analyses confirmed good agreement between OPS imaging and IVM. Thus, OPS imaging is a suitable tool for quantitative assessment of pancreatic capillary perfusion during baseline conditions. A murine model of inflammatory bowel disease was applied to validate OPS imaging against IVM for the visualization of colon microcirculation (42). Postcapillary venular diameter, venular RBC velocity and FCD were analyzed. All parameters correlated significantly between the both methods. The assessment of antivascular tumour treatment using OPS imaging and IVM showed excellent correlation in FCD, diameter of microvessels and RBC velocity between both techniques (35). Validation studies in humans are limited to easily accessible surfaces; fluorescent intravital microscopy is excluded because of need to use fluorescent dye. Thus, OPS imaging has been validated against conventional capillary microscopy in nailfold skin at rest and after venous occlusion in healthy volunteers (37). Results demonstrated that OPS images provided similar values for RBC-velocity and capillary diameter as those measured by conventional capillary microscopy.

Technical limitations

Despite further development and technical improvement in OPS and SDF imaging devices (CYTOSCAN™, MicroScan™ www.microvisionmedical.com) several limitations remain. There are two main conditions for successful OPS/SDF imaging. 1. to create an image of high quality 2. to evaluate the images as quantitatively as possible. Three basic technical limitations have been defined previously (Lindert et al., n d): undesirable pressure of the probe affects blood flow, lateral

movement of tissue precludes continuous investigation of selected microvascular region, and blood flow velocities above 1 mm/s are difficult to measure, thus information on arteriolar flow remains hidden. Stabilizing device which maintains a fixed distance between probe and tissue has been developed to eliminate movement and pressure artefact as much as possible (43). Image analysis according to the principle of spatial correlation allows extending the range of detectable blood flow velocities to over 20 mm/s.

The methods for image analysis and quantification in clinical practise has been reported previously (44), further analysis improvement using flow scoring system has been published recently (33). The technology of OPS-SDF imaging has been incorporated into a small hand-held video-microscope, which can be used in clinical setting. OPS imaging can assess tissue perfusion using FCD parameter, which is a sensitive parameter for determining the status of perfusion to the tissue and also an indirect measure of oxygen delivery. The most easily accessible site in humans is the mouth, where OPS/SDF technology produces excellent images of the sublingual microcirculation (Figure 4). However, several limitations should be acknowledged. Secretions and movement artefacts may impair image quality. In addition, movement artefacts can spuriously interrupt flow in some microvessels. To limit movement artefacts and to decrease the risk of pressure artefacts, use of stabilization devices has been proposed (43). Moreover, current OPS/SDF technology can investigate only tissues covered by a thin epithelial layer and therefore internal organs are not accessible, except for perioperative use. Another major problem with OPS/SDF imaging is the great variability of the vessels measured. Identical site of interest cannot be examined over time in contrast to intravital microscopy in animal experiments (e.g. skinfold chamber). Movement artefacts, uncontrolled application pressure, semi quantitative

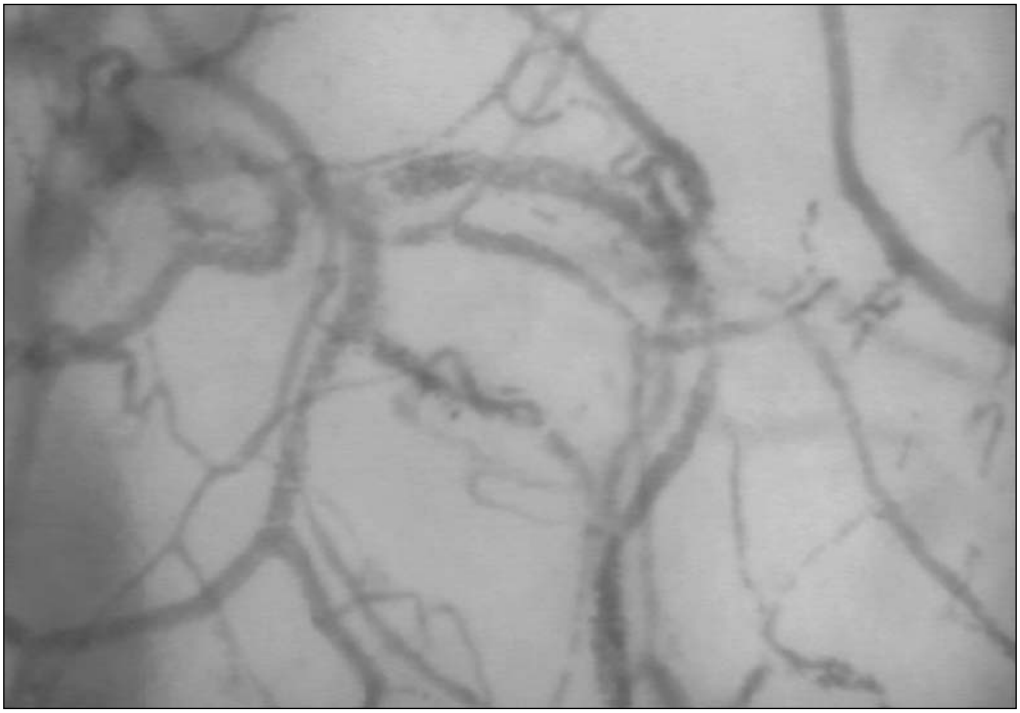

Figure 4: Image of human sublingual microcirculation. SDF imaging of sublingual area in a healthy volunteer (male, 48 years), captured by MicroScan Video Microscope System

measure of perfusion, observer-related bias and also inadequate sedation (if the method is used in clinical setting) may limit quality of obtained data and its correct analysis afterwards. Last but not least, the currently available software (Automated vascular Analysis etc.) is not very useful for routine clinical use, since the analysis requests training period, it is time consuming and must be performed off-line. However, despite all limitations of OPS/SDF imaging, this technology represents a promising non-invasive tool to evaluate microcirculation in both experimental and, maybe even more importantly, in clinical settings, especially in critically ill patients. Further improvements in the technology are pending; they probably bring rapid online analysis of obtained data.

Experimental studies

The sublingual microcirculation and its changes have been studied during various experimental settings, mostly in animal models of sepsis and shock (7). Verdant determined the relationship between sublingual and intestinal mucosal microcirculatory perfusion and his findings support the sublingual region as an appropriate region to monitor the microcirculation in sepsis (45). On the model of endotoxemia in sheep, sublingual microvascular flow indexes were reduced, fluid resuscitation corrected both serosal intestinal and sublingual microcirculation but was unable to restore intestinal mucosal perfusion (46). Effects of the selective iNOS inhibitor with those of norepinephrine (NE) on sublingual microcirculation was studied in a sheep model of septic shock, selective iNOS inhibition had more beneficial effects than NE on microcirculation assessed by SDF imaging sublingually (47). The use of enalaprilat prevented the worsening of sublingual microcirculatory variables in fluid-resuscitated, hyperdynamic model of septic shock (48). Alterations of sublingual microcirculation are present also during experimental haemorrhagic shock and these alterations arise from the first step of the bleeding (49), restoration of microcirculatory flow may be achieved by gelatine and hydroxyethyl starch (50). During cardiac arrest in pigs, sublingual microcirculatory blood flow was highly correlated with macrocirculatory hemodynamics. Administration of epinephrine dramatically decreased microcirculatory blood flow (51). Microvascular blood flow in the sublingual mucosa is also closely related to coronary perfusion pressure during cardiopulmonary resuscitation and predictive of outcome (52). During hypodynamic state of experimental sepsis after infusion of E. coli time-dependent strong correlation exists between sublingual and other microvascular beds, nevertheless, the sublingual mucosa exhibited the most pronounced alterations of microcirculatory flow in comparison with conjunctival, jejunal, and rectal microvasculature (53). Alteration of sublingual microvascular response was also detected during experimental mild hypothermia in an ovine model, where there was a significant decrease in the proportion and density of small perfused vessels, all microcirculatory variables returned to baseline levels during the re-warming phase (54).

Clinical studies

Not surprisingly, probably due to the fact that technology of OPS-SDF imaging has been incorporated into a small hand-held video-microscope, which can be used in clinical setting, much more studies on sublingual microcirculation are in humans, particularly in area of critically ill patients. A growing body of evidence exists on disturbed sublingual microcirculatory functions in relation to increased morbidity and mortality in a wide array of clinical scenarios (12, 13). Changes of sublingual microcirculatory parameters (total and perfused small vessel density) have been recently proposed as an early predictor for critically ill patients (55, 56) and there are several areas in human medicine, where observa-

tion of sublingual microcirculatory bed has been carried out – sepsis, shock, cardiac arrest, effect of various treatments and extreme physiological conditions.

Sepsis and septic shock

In the last few years, an important body of knowledge has been developed showing the pathophysiological relevance of the sublingual microcirculation in the development of multi organ failure associated with sepsis. In addition to the compelling experimental evidence, the development of new videomicroscopic techniques allows now the evaluation of the microcirculation in critically ill patients. Consequently, the sublingual microcirculation can be easily monitored at bedside. Therefore, studies performed in the sublingual area show that severe microcirculatory sublingual alterations are present in septic patients (5). Sepsis results in derangements of microvascular flow, which can be identified in the early stages of this disease. These abnormalities are more marked in the most severely ill patients (57), those changes are present during early course of infection even in preterm infants (3). Sepsis mortality is closely linked to multi-organ failure; impaired microcirculatory blood flow is thought to be a key point in the pathogenesis of sepsis-induced organ failure (58). Images of the sublingual microcirculation during septic shock and resuscitation have revealed that the distributive defect of blood flow occurs at the capillary level. Boerma validated intra-observer and inter-observer reproducibility of OPS images analysis for sublingual bed and concluded that semiquantitative analysis of sublingual microcirculatory flow provides a reproducible and transparent tool in clinical research to monitor and evaluate the microcirculation during sepsis (4). De Backer and coworkers investigated sublingual microcirculation in 50 patients with sepsis by using OPS technique; the density of all vessels was significantly reduced in patients with severe sepsis (4.5 [4.2-5.2] versus 5.4 [5.4-6.3]/mm in volunteers, $p < 0.01$). The proportion of perfused small (< 20 um) vessels was reduced in patients with sepsis (48 [33-61] versus 90 [89-92]% in volunteers, $p < 0.001$), these alterations were more severe in nonsurvivors and they concluded that microvascular blood flow alterations are frequent in patients with sepsis and are more severe even in patients with a worse outcome (44). The sublingual microcirculation was investigated by using OPS in patients with sepsis and organ failure in order to characterize the time course of microcirculatory dysfunction and relation to clinical outcome. Small vessel perfusion improved over time in survivors ($p<0.05$ between survivors and nonsurvivors) but not in nonsurvivors. Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients dying after the resolution of shock in multiple organ failure had a lower percentage of perfused small vessels than survivors (57.4 [46.6-64.9] vs. 79.3 [67.2-83.2]%; $p = .02$) (59). Changes in microcirculation occurred at an early stage in all patients with severe sepsis/septic shock treated with early goal-directed therapy, sublingual perfusion indices were more markedly impaired in nonsurvivors compared with survivors (57, 60). Interestingly, sublingual microvascular derangements in septic shock did not differ between noncytopenic and cytopenic patients (61). Haemodynamic monitoring of septic patients is often impeded by the discrepancy between the macrocirculation and microcirculations parameters, however some correlation between systemic hemodynamic parameters and microcirculation may exist, as shown in a study comparing pulse contour analysis (PiCCO) variables and sublingual microcirculation perfusion indices, where significant correlations were found for current velocity in small venules with systemic vascular resistance ($r(2) = 0.252$, $p < 0.05$) and mean arterial blood pressure ($r(2) = 0.259$, $p < 0.05$), in addition, a significant correlation was also found between the oxygen transport index and the density of small vessels in sublingual area ($r(2) = 0.355$; $p <$

0.05) (62). Recent papers also reveal correlation between lactate level and degree of sublingual microcirculation impairment. In 31 surgical patients significant correlation between the total small vessel density at 1 h and the blood lactate level at 24 h was found (55). During septic shock, increased lactate may play an important role in terms of worsening microcirculatory abnormalities, patients without hyperlactatemia presented higher proportion of perfused vessel and microvascular flow index (63). Changes in sublingual microcirculation during sepsis were identified also in children and infants (3, 64). To summarize, the main characteristics of sublingual microcirculation in patients with septic shock are hypoperfusion and increased flow heterogeneity and nonsurvivors showed more severe alterations than survivors (65).

Effect of various interventions

Fluids, vasopressors/inotropes during sepsis and organ support techniques are (together with the control of infection source) key elements of treatment in all patients with severe sepsis and septic shock. Each of these components were extensively studied with regard to their effect on microcirculation during past years, however mainly in experimental setting and unfortunately only few human studies have been published so far. Early protocol directed resuscitation (including fluid administration) was associated with reduced organ failure at 24 h and results support the hypothesis that targeting the microcirculation distinct from the macrocirculation could potentially improve organ failure in sepsis (60). There is ongoing discussion regarding target blood pressure in patients with septic shock (66), increasing MAP above 65 mmHg with norepineprhrine was associated with improved microvascular function, on the other side, the microvascular response may vary among patients suggesting that individualization of blood pressure targets may be warranted (67). Effect of fluid administration on microcirculatory alterations was evaluated in 60 patients with severe sepsis, where fluid administration increased significantly perfused small vessel density, importantly, microvascular perfusion increased in the early but not in the late phase of sepsis and microvascular effects of fluids were not related to changes in cardiac index or mean arterial pressure (68). Dubin compared 6% hydroxyethyl starch (HES) 130/0.4 with normal saline for resuscitation during early goal-directed therapy (EGDT) in 20 septic patients by using SDF, sublingual capillary density was similar in both groups, but capillary microvascular flow index, percent of perfused capillaries, and perfused capillary density were higher in 6% HES (69). The use of hypertonic fluids in patients with septic shock did not improve sublingual microcirculatory blood flow in comparison to isotonic fluid (70). Improvement of microcirculation in patients with severe sepsis may be achieved, however, even by passive leg rising aiming to increase intravascular volume (71). Using vasopressors to maintain blood pressure has been an important part of septic shock, according to experimental results, their use may compromise microcirculatory flow in different areas. To investigate the effect of norepinephrine (NE) on sublingual microvascular flow (SDF) in patients with septic shock, increasing dose of NE was administered to achieve MAP from 60 to 70-90 mm Hg. No changes in sublingual microvascular flow index, vessel density, the proportion of perfused vessels, perfused vessel density, or heterogeneity index were identified during NE infusion (72). Similar study was carried out in 20 septic shock patients where at a MAP of 65 mmHg, norepinephrine was titrated to reach a MAP of 75 mmHg, and then to 85 mmHg, sublingual microcirculation was assessed by SDF imaging. All patients showed severe sublingual microcirculatory alterations failed to improve with the increases in MAP with norepinephrine (69). Adding terlipressin or arginine vasopressin to norepineprhrine (NE) in patients with NE dependent septic shock does not affect sublingual microcirculatory flow (73). Dobutamin

is recommended as an inotropic agent according to Surviving Sepsis Campaign Guidelines. De Backer evaluated effect of dobutamine on microcirculatory alterations in 22 patients with septic shock, dosage of 5 mug/kg.min dobutamine can improve but not restore capillary perfusion in patients with septic shock and these changes are independent of changes in systemic hemodynamic variables (74). Compared to dobutamine, levosimendan improved sublingual microcirculatory blood flow in patients with septic shock, as reflected by changes in microcirculatory flow indices of small and medium vessels (75) Dobutamine, however prevented postoperative decrease of sublingual microvascular blood flow in patients after esophagectomy (76). The administration of hydrocortisone in septic shock results in a modest but consistent improvement in sublingual capillary perfusion (77).

Transfusion as a part of EGDT protocols and Surviving Sepsis Campaign Guidelines was also evaluated in terms of its effect on microcirculation in patients with sepsis and septic shock. An effect of red blood cell transfusion on sublingual microvascular perfusion was studied in 35 patients with sepsis before and 1 hour after transfusion by using OPS imaging. Microvascular perfusion was not significantly altered by transfusion, but there was considerable interindividual variation. The change in capillary perfusion after transfusion correlated with baseline capillary perfusion and red blood cell storage time had no influence on the microvascular response to red blood cell transfusion (78-81). Effect of transfusion on microcirculation probably also depends on baseline microcirculatory status, patients with relatively altered baseline variables (proportion of perfused vessel) tend to demonstrate improvement in perfusion following transfusion, whereas those with relatively normal perfusion at baseline tend to demonstrate either no change or, in fact, a decline in this parameter (82). Mechanical ventilation and PEEP have no general deleterious effects on microvascular perfusion of the sublingual mucosa (83).

Heart failure and cardiogenic shock

Microcirculatory alterations are present in patients with severe heart failure. De Backer evaluated sublingual microcirculation in in 40 patients with acute severe heart failure, including 31 patients with cardiogenic shock, by using OPS and found the proportion of perfused small (< 20 um) vessels was lower in patients with cardiac failure and cardiogenic shock than in control patients (63% [46%-65%] and 49% [38%-64%] vs. 92% [90%-93%], P <.001). The proportion of perfused vessels was higher in patients who survived than in patients who did not survive in all vessels (90% [84%-93%] vs. 81% [74%-87%], P <.05) and in small vessels (64% [49%-68%] vs. 43% [37%-62%], P <.05) (84). Similar results were found in Jung's study evaluating 24 critically ill patients admitted to ICU. Seven patients with cardiogenic shock had lower microflow compared with patients without cardiogenic shock (small $p<0.001$, medium $p<0.001$, large $p=0.003$). Several other diseases, including diabetes and arterial hypertension, age, gender, had no influence on microcirculatory parameters (85). Recent paper by Elbers revealed also microcirculatory abnormalities during atrial fibrillation and succesfull electrical cardioversion improved indices of sublingual microvascular perfusion (86), similarly as with cardiac resynchronization (87). To summarize the key findings of sublingual microcirculation during severe heart failure and cardiogenic shock – there is reduced vascular density and impaired microflow, especially in the smallest vessels (88). Vasopressors, inotropes and intra-aortic balloon pump represent most often therapeutic approaches in patients with severe heart failure and cardiogenic shock. Several studies examined effect of those common interventions with regard to sublingual microcirculation. The first paper evaluating effects of vasopressor therapy on sublingual microcirculation by using OPS was a case report in patients with severe distributive and cardiogenic shock following cardiac surgery,

where vasopressin was used, however despite its strong vasopressor effects vasopressin infusion did not worsen microcirculatory alterations in this patient (89). Effect of nitroglycerine was tested in 17 patients with cardiogenic shock and chronic heart failure. Nitro-glycerine dose-dependently increases tissue perfusion in patients with severe heart failure, as observed by an increase in sublingual perfused capillary density (90). Similar findings were found during intravenous infusion at a fixed dose of nitroglycerine (NTG) 33 microg/min in 20 acute heart failure patients, where even low-dose NTG significantly improved sublingual microvascular perfusion (91). Effect of intra-aortic balloon pump support (IABP) on macrocirculation and sublingual microcirculation (SDF) in patients with cardiogenic shock was studied by Uil, 13 patients were treated with IABP at different assist ratios. Discontinuation of IABP decreased the mean arterial pressure and cardiac index; however, these changes in macrohemodynamics did not significantly influence sublingual perfused capillary density and capillary red blood cell velocity (92). Improved sublingual microcirculatory flow after IABP was described by Jung in 13 patients with cardiogenic shock (93), combining IABP with extracorporeal membrane oxygenation has led in patient with severe refractory cardiogenic shock to further improvement of sublingual microcirculatory flow assessed by SDF imaging (94). Interestingly recent paper by Munsterman describes discontinuing IABP support showed (SDF) an increase of microcirculatory flow of small vessels after ceasing IABP therapy and his observation may indicate that IABP impairs microvascular perfusion in recovered patients (95). Sublingual microcirculation was assessed also during CPR, first report of using SDF imaging during chest compressions revealed persisting capillary flow even during CPR interruption. Indices of microvascular perfusion were low and were relatively independent from blood pressure (96). In cardiosurgery, the use of pulsatile cardiopulmonary bypass (CPB) preserves microcirculatory perfusion throughout the early postoperative period, irrespective of systemic hemodynamics (97), also changes in CPB flow rate within 20% did not alter the sublingual microcirculation (98) on the other side, the use of the miniaturized extracorporeal circulation system is associated with a statistically significant reduction in sublingual microcirculatory hypoperfusion compared with the use of the conventional extracorporeal circulation system (99). In off-pump coronary artery bypass, cardiac displacement was accompanied by significant decrease of red blood cell velocity (100). During cardiopulmonary bypass, different effect of various inhalational anesthetic agents on indices of sublingual microcirculation was shown, sevoflurane had a negative effect on the microcirculation, isoflurane decreased vascular density and increased flow, desflurane produced stable effects on the microcirculation (101).

Interesting physiological study was published just recently, effect of high altitude on sublingual microcirculation was evaluated in 24 subjects using side stream dark field imaging, as they ascended to 5300 m.; one cohort remained at this altitude, while another ascended higher (maximum 8848 m). Among other variables, the Microvascular flow index (MFI) and vessel density were calculated. Total study length was 71 days, images were recorded at sea level (SL), Namche Bazaar (3500 m), Everest base camp (5300 m), the Western Cwm (6400 m), South Col (7950 m) and departure from Everest base camp (5300 m; 5300 m-b). Compared with SL, altitude resulted in reduced sublingual MFI in small (<25 microm; $P < 0.0001$) and medium vessels (26-50 microm; $P = 0.006$). The greatest reduction in MFI from SL was seen at 5300 m-b; from 2.8 to 2.5 in small vessels and from 2.9 to 2.4 in medium-sized vessels. The reduction in MFI was greater in climbers than in those who remained at 5300 m – in small and medium-sized vessels ($P = 0.017$ and $P = 0.002$, respectively). At 7950 m, administration of supplemental oxygen resulted in a further reduction of MFI and increase in vessel density (102).

Summary

In humans, and especially in critically ill patients, the evaluation of the microcirculation has long been difficult. Recent years have witnessed the development of new techniques that can either directly visualize or indirectly evaluate microvascular perfusion. Currently, monitoring sublingual microcirculation by OPS/SDF imaging remains the only one possibility how to evaluate patient's microcirculation at the bedside. In humans, further improvement, particularly in area of developing rapid, simple and fully automated analyzing tool allowing quantitative assessment during imaging or immediately may help to identify the patients at risk for developing multiple organ failure linked to insults of various kind. Early detection of microvascular abnormality is a key factor to start early therapeutic intervention to reverse microvascular dysfunction and to achieve better clinical outcome. In experimental setting, observing sublingual microcirculation is an important part of any research focused on the role of microcirculation during various diseases models and to assess effect of different treatment modalities on microcirculation.

Acknowledgements

Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 00179906 and by the programme PRVOUK P37/02.

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