The microcirculatory response during cardiac surgery

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Chapter 2

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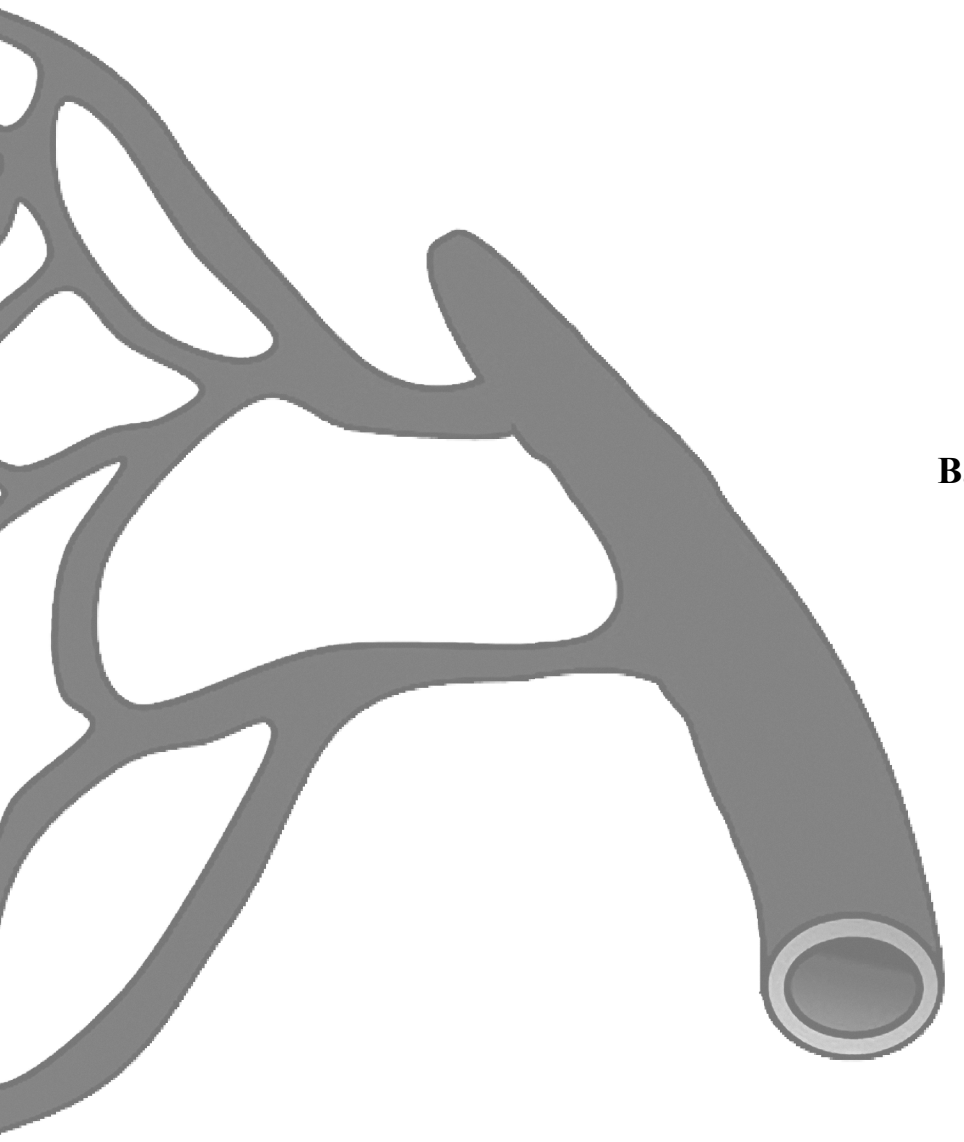

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Introduction

Systemic hemodynamic monitoring is supportive for maintenance of organ perfusion and oxygenation during cardiothoracic procedures, but uninformative with respect to microcirculatory perfusion and oxygenation. Since recent studies suggest that derangement of microcirculatory function may be predictive for organ failure and clinical outcome, adequate monitoring of microcirculatory function is warranted.[1,2] Consequently, there is increasing interest for non-invasive microcirculatory monitoring techniques to define and diagnose microvascular dysfunction in the routine clinical setting.[3]

In addition to the impact of surgery on the systemic circulation, on-pump cardiac surgery with cardiopulmonary bypass is additionally associated with a wide range of changes in systemic hemodynamics and metabolism, which may subsequently affect microcirculatory perfusion and organ function. Although off-pump cardiac surgery is considered to be less detrimental for microcirculatory perfusion as on-pump surgery, positioning of the contracting heart during off-pump procedures may also influence microcirculatory perfusion.

The present clinical review focuses on the distinct alterations in microcirculatory perfusion and oxygenation during on-pump and off-pump cardiac surgery. We particularly describe hemodynamic and metabolic parameters, including blood pressure, hemodilution, hypothermia, hyperoxia, laminar flow and cardiac displacement, which are all of influence on the microcirculatory integrity in the perioperative period. This overview shows that the microcirculation is strongly influenced by systemic alterations during different stages of cardiosurgical procedures.

Perioperative monitoring of microcirculatory function during cardiac surgery

In addition to regional cerebral or somatic tissue oxygenation measurements by near-infrared spectroscopy (NIRS), the availability of Sidestream darkfield (SDF) imaging and reflectance spectrophotometry support visualization and quantification of local microcirculatory perfusion and oxygenation changes during surgery.[3] The sublingual microcirculation is the most commonly used location for SDF imaging and reflectance spectrophotometry, although this microvasculature may not always reflect microvascular alterations in other, more vital organs.[4] Others however showed that, despite the distance of the sublingual circulation to the heart and central circulation, the sublingual microcirculation is a well-established site to

investigate the effects of disease and therapy on microvascular function.[5,6] Moreover, changes in sublingual microcirculatory perfusion are well correlated with alterations in gastric and intestinal beds.[5,6] Alternatively, the rectal microcirculation has recently been proposed as measurement site that is more closely related to the gastrointestinal circulation.[7]

SDF imaging, and its predecessor Orthogonal Polarization Spectral imaging (OPS), is a technique to study human sublingual mucosal microcirculation.[8,9] Additionally, sublingual reflectance spectrophotometry measures the blood oxygenation level at a mucosal level in the terminal network of the microcirculation under the tongue, but this technique is only scarcely described for perioperative microvascular evaluation.[10-12] In contrast to the local measurement dimensions of SDF and reflectance spectrophotometry, regional oxygenated blood is measured using NIRS, which penetrates deeper cerebral or muscular tissue layers.[13] All three techniques are used in the clinical setting and provide specific information with regard to end-organ perfusion.

SDF

SDF imaging is an optical modality for visualization of microcirculatory perfusion that is incorporated in a hand-held microscope containing a light guide and a magnifying lens (Microscan; Microvision Medical, Amsterdam, the Netherlands).[14] For SDF imaging, illumination is provided by surrounding a central light guide with concentrically placed green light-emitting diodes to provide SDF illumination. The lens system located in the core of the light guide is optically isolated from the illuminating outer ring, thereby preventing the microcirculatory image from contamination by tissue surface reflections. Light from the illuminating outer ring of the SDF probe penetrates tissue and subsequently illuminates tissue-embedded microcirculation by scattering. This leads to images where red blood cells are depicted as dark moving globules against a bright background. To improve the imaging of moving structures, such as flowing red blood cells, the light-emitting diodes provide pulsed illumination in synchrony with the recording frame rate. This stroboscopic imaging partially prevents smearing of moving features, such as flowing red blood cells, and motion-induced blurring of capillaries due to the short illumination intervals.[14]

Reflectance spectrophotometry

Reflectance spectrophotometry (RS; “oxygen to see”; O2C; Lea Medizintechnik, Germany) measures microcirculatory blood oxygen saturation and hemoglobin content.[15,16] This technique illuminates tissue with visible white light. Analysis of the spectrum of

backscattered light enables the calculation of the tissue optical absorption spectrum. The O2C device determines the hemoglobin oxygen saturation (HbO_2) based on differentiating absorption spectra of oxygenated and deoxygenated hemoglobin. Oxygenated hemoglobin has two absorption peaks in the visible spectrum, centered on 542 and 577 nm, while deoxygenated hemoglobin has only one absorption peak centered on 556 nm. The total optical absorption is used to reflect the total tissue hemoglobin content. Hence, by scaling the measured absorption spectrum between the known absorption spectra of oxygenated and deoxygenated hemoglobin, the hemoglobin oxygen saturation can be determined. In addition to the sublingual microcirculation, reflectance spectrophotometry is additionally used to clinically measure myocardial oxygenation[17] or gastric mucosal oxygenation.[18]

NIRS

Frontal skull near-infrared spectrometry (NIRS; NIRO-300; Hamamatsu, Japan) is mainly used for transcranial cerebral oxygen saturation, especially during cardiac surgery.[13] Near infrared light wavelengths allow transcranial measurements of oxygen saturation. Four wavelengths of light (775, 810, 850, and 910 nm, respectively) are delivered by four pulsed laser diodes, and scattered light is detected by three closely placed photodiodes. The cerebral tissue oxygenation index (TOI) is calculated by the formula TOI = O_2Hb/Hb (oxygenated hemoglobin (O_2Hb) divided by the total hemoglobin concentration). Among the abovementioned techniques, NIRS is the most frequently used surgical procedures, in particular when decreases in cerebral oxygenation are expected. The cerebral application of NIRS in cardiac surgery for neurocognitive monitoring has extensively reviewed by others and is beyond the scope of this review.[19-21]

Functional microcirculatory parameters

The measurement and quantification of sublingual microcirculatory function can be divided into perfusion or oxygenation parameters. The combination of perfusion and oxygenation measurements provides an integrative overview of microcirculatory behavior, but requires the combined use of different microcirculatory monitoring techniques.[8-11]

Microcirculatory perfusion parameters

The perfused vessel density (PVD) is an indicator for the proportion of perfused vessels in the microcirculation in relation to the total vessel density.[22] The microcirculatory flow index

(MFI) is as semi-quantitative determinant of the predominant flow pattern in a certain area of the microcirculation. The MFI ranges from no flow (0), sluggish flow (1), intermittent flow (2) and continuous flow (3).[23] Space-time diagrams provide red blood cell velocities in the microcirculation by calculation of the diagram-slopes.[24]

Microcirculatory oxygenation parameters

The $u\text{HbO}_2$ is a functional indicator of oxygen delivery to the microcirculation and subsequently the cells. A high $u\text{HbO}_2$ is associated with oxygen off-loading insufficiency by the erythrocytes due to oxygen diffusion limitation caused by a diminishment of the number of perfused microvessels. A low $u\text{HbO}_2$ is associated with oxygen delivery insufficiency due to oxygen convection limitation caused by flow disturbances (MFI 0, 1 or 2) in the microvessels. The regional tissue oxygen index (TOI) is an indicator of the oxygen availability in the deeper layers of an organ. A high TOI indicates sufficient oxygen in the tissue, and a low TOI the opposite.

Specific hemodynamic and metabolic alterations during on-pump cardiac surgery

The switch from physiological, systemic perfusion to extracorporeal circulation using a heart-lung machine is associated with a sudden change in the nature of the circulatory profile. Among others, these changes include hypotension, hemodilution, hypothermia, hyperoxemia, cardiac arrest and a change from pulsatile to continuous, laminar blood flow. The hemodynamic and metabolic effects associated with extracorporeal circulation may lead to reduced oxygen delivery to vital tissues, functional shunting of the microcirculatory circulation as reflected by the fall-out of red blood cell-carrying capillaries, and enhanced venular flow. These observations suggest diffusional limitation of oxygen transport pathways to the organ tissue. Here we describe the effect of these hemodynamic and metabolic alterations on microcirculatory perfusion and oxygenation.

Hypotension

A reduction in blood volume due to the transition to extracorporeal circulation, in combination with the systemic inflammatory response, is associated with a decrease in blood pressure and may lead to hypotensive episodes. During cardiopulmonary bypass, the arterial pressure is generated by means of pump flow regulation. The pump is typically set to reach a flow of 2.2 - 2.4 L/m^2, which generates a volume output of approximately 4 L/min. This may

however be insufficient to maintain a mean arterial pressure of 60 mmHg, requiring volume therapy or pharmacological interventions. Volume therapy interventions include Trendelenburg positioning, passive leg raising or a fluid challenge. Pharmacological correction of hypotension during extracorporeal circulation is often based on the administration of a strong short-acting alpha–adrenergic vasoconstrictor, like phenylephrine.

There is an ongoing debate whether systemic hypotension affects microcirculatory perfusion. Despite a ketanserin-induced blood pressure reduction, Elbers et al. showed no effect on the perfused capillary density in normovolemic cardiosurgical patients.[25] Indeed, in a review by De Backer et al., the relation between system hemodynamics and microcirculatory perfusion was described as relatively loose, especially within the physiological range of cardiac output and blood pressure.[26] However, in case of severe blood pressure derangements, microcirculatory perfusion is additionally affected as was recently shown by two cases of nitroglycerin-induced hypotension. Nitroglycerin-induced vasodilation was associated with an initial increase in the arteriolar diameter and microcirculatory flow, and followed by a reduction in the microvessel blood velocity during the hypotensive phase.[27]

Both volume and pharmacological interventions to correct hypotensive episodes may affect microcirculatory perfusion. Passive leg raising, which induces a fluid shift and increases systemic blood pressure, improved sublingual microcirculatory perfusion in preload responsive severe septic patients.[28] The effects of volume therapy on microvascular recruitment are however difficult to unravel, as they include a blood pressure-modulating and hemodilution component. A recent review by Boerma et al. suggested that an increase in blood pressure of patients with septic shock by vasoactive agents may even be unbeneficial for microcirculatory perfusion in case of a mean arterial pressure exceeding 65 mm Hg.[29] Indeed, a 20 mmHg increase in systemic blood pressure by phenylephrine was associated with depressed sublingual small vessel blood flow while medium-sized vessels were unaffected.[30] These findings suggest that, in case of a relatively normal systemic blood pressure, volume challenges and vasoactive substances are relatively ineffective as modulators of microcirculatory perfusion. Further studies are warranted to reveal new therapeutic strategies for the recruitment of microcirculatory perfusion and oxygenation during hemodynamic derangements.

Hemodilution

Extracorporeal circulation is associated with hemodilution due to the mixture of circulating blood with 1.5-2.0 liters of pump priming solution that result in a reduction in hematocrit values of 28-30 before surgery to 20-24 during cardiopulmonary bypass. The reduction in hematocrit due to the addition of crystalloid solutions is additionally associated with decreased blood viscosity. Visualization of capillary perfusion by SDF imaging is mainly based on the passage of red blood cells through microvessels, and this is therefore significantly reduced in case of a lower blood viscosity. Since pressure-driven microcirculatory perfusion is lowered during a reduction of longitudinal resistance associated with low blood viscosity, red blood cells have difficulty entering high resistance vessels. Indeed, we recently showed that red blood cell transfusion after cardiac surgery, as compared with gelatin-based volume expansion or non-resuscitated patients, increased medium-sized vascular density, red blood cell content and oxygenation in the microcirculation, while the flow index remained unchanged.[32] Others showed that blood transfusion enhanced systemic circulation and oxygen-carrying capacity while improving sublingual microcirculatory density and oxygen saturation in the absence of alterations in perfusion velocity.[12]

The importance of blood viscosity in maintaining functional capillary density was shown in experimental studies using hamsters by Cabrales and Tsai, in which they increased blood viscosity while maintaining low hematocrit by adding highly viscous colloids.[32,33] They further showed that the deleterious effects of a reduced functional capillary density due to hemodilution could be reversed by an increase in blood viscosity.[32,33] The beneficial effects of increased blood viscosity are especially attributed to an improvement in shear stress, nitric oxide production and vasoreactivity.[34] In particular, although hemodilution may be expected to be of no consequence for microcirculatory perfusion due to the compensatory increase in cardiac output, extreme hemodilution is however pathophysiological due to the inability of the cardiovascular system to transmit sufficient central pressure to the microcirculation for the maintenance of functional capillary density, which is a linear function of capillary pressure.[34] Although the association of a reduction in hematocrit with adverse outcome and organ dysfunction is broadly discussed, our insight in the pathophysiological mechanisms are limited, the presence of an oxygen debt has been suggested as the main cause. The presence of the oxygen debt as a result of increased diffusional distance from filled capillaries to the cellular system instead of a reduced oxygen carrying capacity of blood during low hematocrit states should therefore be further investigated.

Hypothermia

Hypothermia during extracorporeal circulation reduces myocardial oxygen consumption, thereby preserving cellular function. In particular, in some cases of extracorporeal circulation the body temperature is decreased to 32-35° Celsius within 15 minutes after the onset of cardiopulmonary bypass. Hypothermic tissue with a temporarily reduced oxygen demand may affect microcirculatory perfusion, and consequently lead to a redistribution of microcirculatory flow to regulate the amount of necessary oxygen in the terminal microcirculatory network. The number of clinical studies focusing on the effects of hypothermia on microcirculatory perfusion and oxygenation are however limited, and mostly focused on deep hypothermic arrest. A recent experimental study in sheep under normovolemic conditions showed that a 6-hour period of mild hypothermia (34^{o}C) was associated with a reduction of ventricular function, oxygen extraction and microvascular flow when compared to normothermia, which suggested that mild hypothermia may impair tissue oxygen delivery through inappropriate distribution of capillary flow.[35] Hypothermia may therefore contribute to an imbalance between oxygen delivery and demand, but clinical studies should further confirm this finding.

Hyperoxemia

Hyperoxemia (20-30 kPa) is applied to compensate for pulmonary bypass and to enhance oxygen delivery to tissues during extracorporeal circulation. However, several lines of investigation have shown that hyperoxemia may have unbeneficial effects, including a decrease in microvascular functional capillary density. In particular, hamster experiments showed a decrease in functional capillary density under conditions of hyperoxemia, assuming vasoconstriction or shunting proximal to the capillary network.[36,37] Tsai et al. explained this phenomenon by demonstrating vasoconstriction of arterioles without a concomitant reduction in oxygen delivery in the microcirculation, which would suggest a compensatory mechanism that is regulated upstream of the capillary level.[37] There are currently no clinical studies that evaluated the effects of hyperoxemia on the human microcirculation using SDF imaging or reflectance spectrophotometry.

Cardiac arrest

Cardiopulmonary arrest to enable coronary artery bypass grafting is considered as period of myocardial ischemia. The direct effects of hypothermic cardiac arrest on microcirculatory perfusion were studied in patients undergoing aortic arch reconstruction. Cardiac arrest was

associated with an immediate shutdown of sublingual microvessel perfusion, while flow in larger microvessels persisted.[38] This is paralleled by a cerebral decrease in oxygenated hemoglobin, increase in deoxygenated hemoglobin and a reduction in the cerebral oxygen extraction ratio.[39] Impaired microcirculatory perfusion and oxygenation is however recovered after restoration of myocardial function and systemic blood flow.

Laminar flow conditions

The switch to extracorporeal circulation is associated with a change from pulsatile to continuous laminar flow conditions. Several studies evaluated whether restoration of pulsatile flow during extracorporeal circulation may improve microcirculatory perfusion and oxygenation, but current findings are still inconclusive. On one hand, pulsatile flow during cardiopulmonary bypass seemed to be beneficial as reflected by reduced markers of endothelial damage and improved gastric mucosal oxygenation and tonometry.[40,41] In particular, laminar flow CPB was associated with a greater reduction in gastric wall blood flow compared to a pulsatile group, while there was no difference in gastric mucosal oxygenation between groups.[41] In contrast, others found that short-term pulsatile flow during cardiopulmonary bypass was not beneficial for microcirculatory perfusion[42] or cerebral oxygenation[43] when compared to a laminar flow conditions. Whether restoration of pulsatility during extracorporeal circulation is advantageous for microcirculatory perfusion and oxygenation remains to be elucidated, especially as the study design of both recent studies was suboptimal in order to show the lack of benefits of pulsatile flow during cardiopulmonary bypass.[44]

The microcirculatory response during on-pump or off-pump cardiac surgery

On-pump cardiac surgery

Cardiopulmonary bypass is associated with hemodynamic and metabolic alterations that may influence microcirculatory perfusion and oxygenation. Although individual hemodynamic and metabolic parameters such as hypotension, hemodilution and hypothermia may have distinct effects on microcirculatory behavior, most clinical studies focus on the overall accumulation of microcirculatory responses during cardiopulmonary bypass.

We earlier showed that the imposition of extracorporeal circulation during arterial bypass grafting reduced functional microvascular capillary density and increased venular blood

velocity.[35] We further observed a rise in hemoglobin oxygen saturation, possibly due to a defect in oxygen extraction.[11] Others showed that on-pump cardiac surgery is associated with a decreased proportion and density of perfused small vessels, and these observations are irrespective of hemodynamic changes.[45-48] In contrast, Maier et al. demonstrated that initiation of cardiopulmonary bypass did not alter sublingual microcirculatory perfusion, while an additional phenylephrine-induced systemic blood pressure increase reduced small vessel blood flow and augmented tissue hemoglobin oxygenation.[30] Others showed that the rectal microvascular flow index and the proportion of perfused vessels was almost normal at 30 minutes following cardiac surgery.[7] Using reflectance spectroscopy during different phases of on-pump coronary artery bypass grafting, it was further shown that tissue oxygenation is augmented after aorta cross-clamping and reperfusion, while it decreases during cardiac arrest.[17] Moreover, cardiopulmonary bypass is associated with a reduction in palmar tissue oxygenation.[49] The cardiopulmonary bypass-associated changes in systemic, microvascular and hemorheologic variables are presented in table 1.

Off-pump cardiac surgery

Cardiac displacement during off-pump coronary artery bypass graft (OPCABG) surgery for posterior and anterolateral graft anastomoses is associated with a reduction in cardiac output of 15-45%. The reduction in cardiac output may be associated with cessation of microcirculatory blood flow and decreases in microcirculatory hemoglobin oxygenation. Indeed, we earlier showed that off-pump procedures are associated with distinct alterations in microcirculatory function when compared with on-pump surgery. In particular, cardiac displacement during off-pump surgery did not affect capillary density, but resulted in cessation of microcirculatory flow due to a reduced entry of red blood cells into the microvasculature, and decreased hemoglobin oxygen saturation in parallel to the sudden decrease in cardiac output as a result of cardiac displacement.[10,11] The results in off-pump patients during cardiac positioning show that oxygen availability in the sublingual microcirculation is reduced due to the failure of red blood cells entering the capillaries, instead of a redistribution of blood during hemodilution in on-pump patients. Moreover, cardiac displacement is responsible for a reduction in cerebral cortical oxygenation that is reversed by returning the heart to its natural position.[50] The overall effects of off-pump cardiac surgery on systemic, microvascular and hemorheologic variables are shown in table 1.

Table 1. Effects of on-pump and off-pump cardiac surgery on systemic, microcirculatory and hemorheologic variables.

	Cardiopulmonary bypass *(on-pump surgery)*	Cardiac displacement *(off-pump surgery)*
Systemic variables		
Temperature	↓	=
Hemoglobin	↓	=
Cardiac output	↑	↓
Blood pressure	↓	↓
Oxygen delivery	↓	↓
Microcirculatory variables		
Hemoglobin concentration	↓	↓
Hemoglobin O_2 saturation	↑	↓
Red blood cell velocity	↑	↓
Perfused capillary density	↓	=
Hemorheologic variables		
Hematocrit	↓	=
Blood viscosity	↓	=

Integrative monitoring of microcirculatory function during cardiac surgery

Despite the available literature, a better understanding of derangements in microcirculatory perfusion and tissue oxygenation is required to avoid microcirculatory dysfunction during cardiac surgery. An integrative evaluation of sublingual microvessel perfusion in combination with microcirculatory oxygenation provides novel insight in the effect of cardiac iatrogenic maneuvers on microcirculatory perfusion and blood and oxygen supply. Moreover, integrative perioperative monitoring of the microcirculation may be beneficial to obtain a better definition of microcirculatory dysfunction during acute events like cardiac surgery. The surgical setting is an interesting field to gain more insight in microvascular derangements, as surgical procedures are based on well-defined procedures and interventions and, the effect of anesthetic and surgical management on microcirculatory function is predictable. Moreover, perioperative systemic hemodynamic alterations are acute and causative for microcirculatory effects, and subsequent corrections of these alterations are acutely reflected by the microcirculation. The lack of systematic, large cohort patient studies however prohibits a

robust conclusion with respect to microcirculatory responses to on-pump and off-pump surgery, and warrants further investigation.

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