Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: A pilot study

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Objective: Complications after cardiac surgery may involve multiple organ failure, which carries a high mortality. Development of multiple organ failure may be related to impaired microcirculatory perfusion as a result of systemic inflammation. Microcirculatory blood flow alterations have been associated with impaired outcome. We investigated whether these alterations occurred before, during, and after coronary artery bypass grafting.

Methods: We observed 25 consecutive patients who underwent elective coronary artery bypass grafting with cardiopulmonary bypass. The sublingual microcirculation was investigated using side-stream dark-field imaging. Side-stream dark-field imaging was performed before (baseline), during, and after surgery. Microvascular blood flow was estimated with a semiquantitative microvascular flow index in small, medium, and large microvessels. Changes in microvascular flow were tested with Wilcoxon signed rank test.

Results: Median microvascular flow index of medium blood vessels decreased after starting cardiopulmonary bypass relative to that after anesthetic induction (2.6, interquartile range 1.6–3.0, vs 3.0, interquartile range 2.8–3.0, $P = .02$). There was a trend toward decreased microvascular flow index of small and large vessels relative to baseline ($P = .08$ and $P = .05$, respectively). Decreases in microvascular flow index occurred irrespective of changes in systemic blood pressure. After each patient's return to the intensive care unit, microvascular flow index increased and normalized in all microvessels.

Conclusion: For the first time, sublingual microvascular blood flow alterations have been observed during cardiopulmonary bypass–assisted coronary artery bypass grafting.

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Coronary artery bypass grafting (CABG) is a well-established treatment modality for patients with severe ischemic heart disease. In on-pump CABG surgery, the circulation is preserved with an extracorporeal cardiopulmonary bypass (CPB) device while the heart is arrested by a cardioplegic solution. These days, excellent results are obtained with both on-pump and off-pump cardiac surgery, with low morbidity and mortality.¹ Nevertheless, cardiac surgery, especially CPB-assisted cardiac surgery, is associated with activation of inflammatory mediators and systemic inflammatory response syndrome. This inflammatory response, together with procedure-related formation of microemboli, may result in capillary dysfunction

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
IQR	= interquartile range
MAP	= mean arterial pressure
MFI	= microvascular flow index
SDF	= side-stream dark-field

and postoperative multiple organ dysfunction.² Organ dysfunction after cardiac surgery is known to be associated with prolonged postoperative intensive care unit stay and high 30-day and long-term mortalities.³ A relationship between microcirculatory dysfunction and the degree of organ failure has previously been suggested in patients with sepsis.⁴ In view of the inflammatory response induced by cardiac surgery, we investigated microcirculatory blood flow alterations during and after CPB-assisted cardiac surgery.

Materials and Methods**Study Design**

We conducted an observational pilot study at our university hospital. Data collection was based on side-stream dark-field (SDF) imaging and on routine measurements. The institutional ethical committee approved the protocol, and informed consent was obtained from each patient.

Patients

Twenty-five consecutive patients scheduled for elective CABG with CPB were included. Before the operation, in-hospital mortality risk was predicted with the EuroSCORE.^{5,6}

Anesthesia, Surgery, and CPB Management

Anesthesia was intravenously induced with midazolam (0.15–0.25 mg/kg), sufentanyl (1 µg/kg), and pancuronium bromide (0.1 mg/kg), to which an intravenous bolus of enoximone (0.25 mg/kg) was added. Dexamethasone (1 mg/kg) was intravenously administered at the discretion of the attending anesthesiologist. Phenylephrine hydrochloride was given when mean arterial pressure was below 60 mm Hg. A 9.5F five-lumen central venous catheter (Multicath; Laboratoires Pharmaceutiques Vygon, Ecouen, France) was inserted into the right internal jugular vein. A urinary bladder catheter with temperature measurement feature (179360CH14; Willy Ruesch AG, Kernen, Germany) was inserted. Bladder temperature was regarded as an estimate of body core temperature. In the operating room, anesthesia was maintained with intravenous midazolam (0.1 mg/[kg · h]) and intravenous sufentanyl (0.5–1.0 µg/[kg · h]), to which inhalation of sevoflurane (1%–2% by volume) during the prebypass period might be added according to the discretion of the attending anesthesiologist. Nonpulsatile CPB (Stockert-Shiley Multiflow Roller Pump; Soma Technology Inc, Cheshire, Conn) was established through a standard median sternotomy with aortic root and right atrial cannulation. Surgery was performed under mild hypothermia (32°C). After aortic crossclamping, antegrade ice-cold St Thomas' hospital cardioplegia was administered. Anticoagulation was established with intravenous heparin (3–4 mg/kg)

given 10 minutes before initiation of CPB. Target activated clotting time was 440 seconds. At the end of CPB, anticoagulation was antagonized with intravenous protamine sulfate (4 mg/kg). Hematocrit was kept above 0.20 L/L. After surgery, patients were actively rewarmed with warm-air blankets until bladder temperature reached 36.5°C.

Macrohemodynamic Monitoring

Arterial and central venous pressure were monitored invasively in all cases. Continuous cardiac output measurements were performed in only 16 of 25 cases because the PiCCO system was not always available. In these patients, before induction a 4F thermistor-tipped catheter (PV2014L50LGW Pulsioath; Pulsion Medical Systems AG, Munich, Germany) was inserted under local anesthesia into the left radial artery. This catheter was then connected to a monitor (PiCCO Plus; Pulsion Medical Systems). After calibration by transcardiopulmonary thermodilution, cardiac output was continuously measured.

Microcirculatory Assessment and Analysis

The SDF device (MicroScan; MicrovisionMedical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of microcirculatory blood flow.⁷ SDF imaging is the successor technology adapted from orthogonal polarization spectral imaging, which was validated previously.^{8–10} Sublingual SDF imaging and subsequent semiquantitative analysis were performed as reported previously.⁹ In short, steady video images with duration of at least 20 seconds were obtained after gentle removal of saliva by a gauze, avoiding pressure artifacts as much as possible. Pressure artifacts can be noticed by an alteration of flow velocity in the vessels under investigation, depending on application of pressure with the tip of the probe. Video sequences were stored and analyzed blindly and in random order by an investigator not involved in data collection. Each SDF video clip was divided into four equal quadrants. Quantification of flow (0 for no flow, 1 for intermittent flow, 2 for sluggish flow, and 3 for continuous flow) was scored per quadrant in small (diameter 10–25 µm), medium (25–50 µm), and large (50–100 µm) microvessels, as applicable. This score, the microvascular flow index (MFI), was the sum of each quadrant's scores divided by the number of quadrants in which the vessel type was visible.

The first SDF measurements were performed the day before surgery (T0). Thereafter, sublingual microvascular perfusion was determined in the following measurement periods, successively: after anesthetic induction (T1), on nonpulsatile CPB immediately after complete administration of cardioplegia (T2), postoperatively just after admission to the intensive care unit (T3), and when body core temperature had reached 36.5°C (T4).

Statistical Analysis

Variables that were not normally distributed, including MFI, are presented as median with interquartile range (IQR, 25th–75th percentiles). Categorical variables are presented as absolute number with percentage. Global hemodynamic data are presented as mean ± SD. Analysis of variance (1-way) and subsequent Bonferroni test were used to establish differences in global hemodynamic variables between the successive measurement periods. Changes in microvascular flow were tested with Wilcoxon signed rank test. Linear correlations between macrocirculatory and microcirculatory parameters were calculated with the Spearman correlation test. The Mann-Whitney test was used to assess differences between subgroups.

TABLE 1. Characteristics of the study population (n = 25)

Age (y, median and IQR)	65 (61-74)
Male (No.)	20 (80%)
Preoperative risk factors (No.)	
Hypertension	17 (68%)
Current smoking	6 (24%)
Dyslipidemia	10 (40%)
Diabetes mellitus	6 (24%)
Logistic EuroSCORE (%; median and IQR)	1.5% (1.2%-4.0%)
Type of surgery	
Isolated CABG procedure	20 (80%)
CABG plus valve surgery	3 (12%)
CABG plus LV reconstruction procedure	1 (4%)
CABG plus valve surgery plus LV reconstruction procedure	1 (4%)
Total anastomoses	
Left ITA	29*
Right ITA	10
Venous bypass	53
Cardiopulmonary bypass duration (min, median and IQR)	102 (94-140)
Aortic crossclamp time (min, median and IQR)	65 (56-84)

IQR, Interquartile range; CABG, coronary artery bypass grafting; LV, left ventricular; ITA, internal thoracic artery. *In some cases, a single left internal thoracic artery graft was used to prepare more than one anastomosis.

Results

Study Population

Twenty-five consecutive patients undergoing elective CABG were enrolled in the study. Twenty of them underwent isolated CABG. Table 1 shows the patients' characteristics. Two patients died. An 84-year-old man died in the intensive care unit of failure of the heart and the kidneys 12 days after CABG and mitral valve repair. A 77-year-old male man undergoing CABG, aortic valve replacement, and left ventricular reconstruction died in the operating room of progressive cardiac pump failure despite optimal treatment.

Global Hemodynamics

After induction of anesthesia mean arterial pressure (MAP) decreased by about 25% (T1 vs T0, $P = .001$). Minimal MAP was observed after starting CPB: 63 ± 11 mm Hg versus 75 ± 17 mm Hg after induction ($P = .05$). MAP recovered after surgery and remained stable during rewarming (Table 2).

The indexed flow delivered by the heart lung machine was 2.5 ± 0.3 mL/(min · m²). This index was similar to the preoperative cardiac index measured by the PiCCO system (2.8 ± 0.6 mL/(min · m²)). Postoperatively measured cardiac index values (3.2 ± 0.7 mL/(min · m²)) did not differ from preoperative measurements (Table 2).

Central venous pressure after initiation of CPB (7 ± 4 mm Hg) did not change relative to the central venous pressure measured after anesthetic induction (8 ± 4 mm Hg). Higher central venous pressure values were observed, however, after return to the intensive care unit relative to the situation during

CPB (10 ± 2 vs 7 ± 4 mm Hg, $P = .01$; Table 2). Large decreases in hemoglobin concentration and hematocrit occurred during surgery, whereas no elevations in serum lactate were observed during CPB (Table 2).

Microcirculatory Measurements

In general, sublingual SDF imaging was more difficult to perform 1 day before surgery than during anesthesia as a result of movement of the tongue in the nonsedated patient. More pressure artifacts were therefore visible at T0. Preoperative MFIs were 2.8 (IQR 2.0–3.0), 2.5 (IQR 2.0–3.0), and 2.8 (IQR 2.8–3.0) for small, medium, and large microvessels, respectively (Table 2). In 46% of the investigated patients, MFI less than 2.50 for medium microvessels was observed just after initiation of nonpulsatile CPB (T2; Figure 1). This MFI was lower than the microvascular perfusion after anesthetic induction (T2 vs T1, $P = .05$). There was a trend toward a decrease in microvascular perfusion at T2 for small ($P = .08$) and large ($P = .05$) microvessels as well. Postoperative SDF imaging showed fast microvascular blood flow in all microvessels. This resulted in a high MFI in small (3.0, IQR 3.0–3.0), medium (3.0, IQR 2.9–3.0), and large (3.0, IQR 3.0–3.0) microvessels (T3; Table 2). Postoperative MFI had risen to normal values in all microvessels relative to microvascular perfusion assessed during CPB (T3 vs T2, all $P = .02$; Table 2). MFI for all sizes of microvessels did not change after central body temperature had reached 36.5°C (T4 vs T3, all differences not significant; Table 2). Retrospectively, a large decrease in microvascular perfusion during CPB was observed in the patient who finally died of heart and renal failure (patient 1; Figure 2).

Changes in Microvascular Perfusion in Relationship to MAP, Lactate, and Preoperative Risk Factors

We investigated whether impaired microvascular blood flow during CPB was associated with simultaneous decrease in systemic perfusion pressure (ie, MAP). We plotted the change in MFI (T2 – T1) versus change in MAP (T2 – T1). No association was visible ($r = 0.23$, difference not significant).

Two patients had a slightly elevated serum lactate concentration just after surgery, 1.9 and 2.2 mmol/L (upper reference limit 1.7 mmol/L in our laboratory). In both cases, intraoperative hypoperfusion of small and medium microvessels occurred. In the first patient, MFIs at T2 were 2.00, 1.25, and 1.50 for small, medium, and large blood vessels, respectively. In the second patient, these values were 1.00, 1.75, and 1.75, respectively.

There were no significant differences in MFI during CPB for medium blood vessels when patients were stratified according to preoperative risk factors of hypertension ($P = .62$), current smoking ($P = .90$), and diabetes mellitus ($P = .69$). Microvascular blood flow did not differ between patients who underwent

TABLE 2. Global and microcirculatory variables: Evolution through time

	T0	T1	T2	T3	T4
Core body temperature (°C)	37.0 ± 0.4	36.3 ± 0.5	34.2 ± 1.0	34.9 ± 0.7	36.8 ± 0.6
Heart rate (beats/min)	69 ± 16	69 ± 12	—	78 ± 15	84 ± 14
Mean arterial pressure (mm Hg)	101 ± 16	75 ± 17	63 ± 11	83 ± 11	80 ± 14
Central venous pressure (mm Hg)	—	8 ± 4	7 ± 4	10 ± 2	13 ± 4
Cardiac index* (mL/[min · m ²])	—	2.8 ± 0.6	2.5 ± 0.3	3.2 ± 0.7	3.1 ± 0.6
Hemoglobin (mmol/L)	8.7 ± 0.9	7.0 ± 0.9	4.7 ± 0.4	6.1 ± 0.6	6.2 ± 0.5
Hematocrit (L/L)	0.41 ± 0.0	0.32 ± 0.0	0.22 ± 0.0	0.28 ± 0.0	0.29 ± 0.0
Lactate (mmol/L)	—	1.0 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	1.6 ± 0.7
Microvascular flow index					
Small microvessels	2.8 (2.0-3.0)	3.0 (3.0-3.0)	3.0 (1.3-3.0)	3.0 (3.0-3.0)	3.0 (2.9-3.0)
Medium microvessels	2.5 (2.0-3.0)	3.0 (2.8-3.0)	2.6 (1.6-3.0)†	3.0 (2.9-3.0)	3.0 (2.6-3.0)
Large microvessels	2.8 (2.8-3.0)	3.0 (2.8-3.0)	3.0 (1.7-3.0)	3.0 (3.0-3.0)	3.0 (2.9-3.0)

All data except microvascular flow index are presented as mean ± SD; microvascular flow index is shown as median with interquartile range. T0, 1 day before surgery; T1, after anesthetic induction; T2, after cardioplegia during CPB; T3, arrival to intensive care unit; T4, core body temperature greater than 36.5°C achieved. *Cardiac index values were obtained for 16 of 25 patients. † $P < .05$ versus T1.

isolated CABG and those operated on for combined heart disease ($P = .33$).

Discussion

For the first time, a 2-dimensional imaging technique, in this case SDF imaging, was used to investigate the human microcirculation during cardiac surgery. We demonstrated the feasibility of using SDF imaging to monitor the microcirculation

at the bedside, as well as in the operating room. We found that sublingual microcirculatory flow decreased during CPB. This finding applied significantly to medium blood vessels. MFI recovered in the postoperative state.

Two patients died. In our opinion, the case of patient 1 is more interesting than that of patient 2. We think that the main cause of death for patient 2 was acute heart failure after cessation of CPB (duration 360 minutes). In contrast, the microcirculation may have played an important role in the bad outcome of patient 1. Impaired microcirculation was also observed in both of the patients who had elevated postoperative lactate levels. Although all these cases represent only case observations, and other factors than the microcirculation may have played significant roles, these examples indicate that perioperative optimization of macrohemodynamic parameters (such as blood pressure) is not always sufficient to optimize perfusion at the microvascular level.

Several studies have reported on the use of tonometry to assess microcirculatory function during cardiac surgery. These studies all suggested impaired intestinal perfusion during cardiac surgery, although it is still questionable whether a resuscitation strategy that is based on tonometry measurements is more beneficial than are conventional strategies that are based on classic indices of perfusion.¹¹⁻¹³ We used a novel imaging modality in our study, and the results are consistent with these tonometry reports. We found that the decrease in microvascular perfusion was independent of changes in systemic perfusion pressure, which is in line with previous experimental and clinical data in sepsis.¹⁴⁻¹⁷

Limitations

Although SDF imaging is an improved technique relative to orthogonal polarization spectral imaging, it still has its limitations. Pressure artifacts hinder the analysis of the images captured from a nonsedated patient, who moves the tongue

Figure 1. Changes in perfusion of medium microvessels with time (n = 25). Bars indicate distribution of patients who had preserved microcirculation (arbitrarily defined as microvascular flow index ≥ 2.5 ; open bars) versus those who had impaired microcirculation (microvascular flow index < 2.5 ; black bars). In 46% of patients, microvascular flow index less than 2.5 was seen after initiation of cardiopulmonary bypass (CPB; T2). This MFI was lower than microvascular perfusion after anesthetic induction (T1). T1, After anesthetic induction; T2, cardiopulmonary bypass; T3, arrival at intensive care unit (ICU); T4, body temperature (Temp) greater than 36.5°C. Asterisk indicates $P = .05$ versus T1; crosshatch indicates $P = .01$ versus T2.

Figure 2. Detailed perioperative macrohemodynamic and microhemodynamic parameters through time of 2 patients who died. Both patients had higher than average mortality risk. Patient 1 died in intensive care unit of multiple organ failure. Retrospectively, hypoperfusion of microcirculation was present after anesthetic induction as well as after initiation of cardiopulmonary bypass. In contrast, sublingual microcirculation was preserved in patient 2, who died in operating room of progressive cardiac failure after cessation of cardiopulmonary bypass. YOM, Year-old male; CABG, coronary artery bypass grafting; MVR, mitral valve repair; MFI, microvascular flow index; CPB, cardiopulmonary bypass; Temp, body temperature; HR, heart rate; MAP, mean arterial pressure; AVR, aortic valve replacement; LVR, left ventricular restoration.

and the adjacent sublingual area continuously. For the same reason, pressure artifacts thwart comparisons between images captured 1 day before surgery (T0) and images taken after the patient was sedated (T1 and thereafter). This phenomenon raises the question of which measurement is the true baseline (T0 or T1). A second limitation of 2-dimensional imaging techniques is that movements of tissue and probe make it impossible to record the same selected sublingual area during different measurement periods, resulting in heterogeneous images of the microcirculation. Although quantification partially corrects for this heterogeneity, it makes off-line analysis less easy and emphasizes the importance of blinding the images before final quantification.

Microvascular perfusion did not decrease during CPB in all patients. The period after the start of CPB is an interval in which many factors influence microcirculatory function. Examples of these factors are the switch from pulsatile to nonpul-

satile CPB blood flow, the sudden entrance into the circulation of the CPB priming fluid, continuous changes in hematocrit, cardiac manipulations by the surgeon, and administration of bolus doses of vasoactive drugs. Interpatient differences in these factors may explain in part our heterogeneous results.

Clinical Perspective and Conclusion

The basic task of the cardiovascular system is to provide the metabolic requirements of the tissues. Inadequate perfusion leads to the activation of anaerobic metabolism pathways, oxygen debt, and tissue acidosis.¹⁸ Standard parameters, however, such as cardiac output, blood pressure, heart rate, and amount of diuresis, are limited in predicting the state of the local organ blood supply.¹⁹ Instruments that monitor perfusion at the microvascular level are therefore valuable. It would be interesting to perform a new study in which SDF imaging is combined with tonometry to determine a possible

relationship between the two methods. This was previously done in patients with sepsis.²⁰

In conclusion, SDF imaging is a promising technique to visualize microcirculatory alterations at the bedside, or even in the operating room. In this pilot study, a decrease in microvascular perfusion, not associated with a decrease in systemic perfusion pressure, was observed after the start of nonpulsatile CPB. Further investigations are necessary to confirm these findings and to discover whether the severity and duration of these changes are associated with patient outcome, as was previously demonstrated for sepsis.⁴ A further intriguing question would be whether a resuscitation strategy that is based on, and monitored with, SDF imaging could be beneficial to reduce multiorgan failure after cardiac surgery.

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