Distributive failure in the microcirculation of septic patients
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Chapter 4

Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis

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Abstract

Objective:
To evaluate the relation between sublingual and intestinal microcirculatory alterations in patients with an abdominal sepsis.

Design:
Prospective observational study

Setting:
A 23-bed mixed intensive care unit of a tertiary teaching hospital

Patients:
Twenty-three patients with an abdominal sepsis and a newly constructed intestinal stoma in the study group. Nineteen outpatient healthy individuals with an intestinal stoma and 10 non-sepsis patients with a-less-than-24-hours-old intestinal stoma were included as controls.

Interventions:
none

Measurements and Main Results:
Orthogonal polarization spectral imaging of the sublingual and intestinal microcirculation was performed on day 1 and 3. In addition, parameters of systemic hemodynamics, such as cardiac index, heart rate, blood pressure, central venous pressure and dosages of vasopressor and inotropic agents were obtained. On day 1 there was no correlation of the microvascular flow index (MFI) between the sublingual and intestinal microcirculatory beds (Spearman’s rho (r) = 0.12, 95% CI -0.51-0.31, p =0.59). Furthermore, there was no significant correlation between microcirculatory alterations and parameters of systemic circulation (r ≤ 0.25). On day 3 however, a correlation between sublingual and intestinal microcirculatory flow appears to be restored (r = 0.74, 95% CI 0.28-0.92, p = 0.006), mainly due to a normalisation of flow in both regions.

Conclusions:
On day 1 of an abdominal sepsis there is a complete dispersion of flow, not only between hemodynamic compartments of a different order, but also between the sublingual and intestinal microcirculation. Over time, both sublingual and intestinal MFI tended to normal values.
Introduction

Many years ago Weil and Shubin proposed a classification of shock with special reference to its distributive forms (1). The distributive defect in septic shock has been classically defined as a redistribution of volumes and reflects a defect in vascular regulation in the presence of normal or even supernormal oxygen delivery. However, the precise nature of these distributive alterations has been largely unknown for many decades. In the previous years, research, using Orthogonal Polarization Spectral (OPS) imaging, has revealed that microcirculatory alterations may explain the distributive defects seen in sepsis. Application of this technique (2) in a hand-held device made direct observation of the human microcirculation during sepsis possible. This technique is not only applicable in the sublingual region, but also in other organs like the intestinal tract, for instance when a stoma is available. Microcirculatory abnormalities, and in particular, heterogeneity of flow, are now being recognized as key characteristics in the pathogenesis of organ dysfunction during sepsis (3,4). Combining OPS imaging with other techniques such as sublingual capnometry added to the understanding of the relation between microcirculatory abnormalities and metabolic tissue parameters (5,6). Persistence of such abnormalities were found to be associated with prognosis, in contrast to all the available systemic hemodynamic parameters (7). An important question to be addressed in this approach is to what extent the sublingual region reflects microcirculatory abnormalities in other organs. This is of particular importance, since an inability to extract oxygen as a result of local tissue factors, is considered to be a distinctive quality of septic shock in comparison to other shock models (8,9). In other words, during sepsis there is a local inability to regulate oxygen delivery despite adequate oxygen supply, resulting in tissue hypoxia. Since local, rather than systemic factors seem to determine oxygen consumption, it is imaginable that sublingual microcirculatory abnormalities during septic shock do not reflect alterations in other microvascular beds, nor will it be likely that these microcirculatory abnormalities are correlated with systemic hemodynamic parameters.

In this study we tested the hypothesis that septic shock in humans is characterized by a dissociation not only between the microcirculation and the systemic circulation, but also that each microcirculatory organ system starts to behave individually as loss of integrative control by the systemic circulation and local factors start to dominate (micro)circulatory defects. We tested this hypothesis in patients with an abdominal septic shock and, apart from the sublingual region, a surgical intestinal stoma as a second organ site accessible for OPS microcirculatory imaging.
Chapter 4

Materials and methods

Setting and patient selection.
A single center prospective observational study was performed in a tertiary teaching-hospital with a 23-bed mixed ICU. Between January and September 2004 patients with a new intestinal stoma in the course of abdominal sepsis were included. Patients were only included when the source of the sepsis was confirmed by faecal spill in the abdominal cavity, as observed during the surgical procedure. Cultures of abdominal fluid samples were performed for confirmation. Overt clinical necrosis of the stoma and an age <18 years were contraindications for enrolment.

Furthermore, 2 subsets of patients were included as controls for comparison with the study group on day one. One group consisted of healthy individuals from the surgical outpatient department, with a stoma of at least 3 months old. The other group was formed by non-ICU patients with a less-than-24-hours-old intestinal stoma in the absence of sepsis, according to the Bone criteria (10).

A local ethical and scientific committee approved the study protocol and written informed consent was obtained from the patients or their next of kin, according to Dutch and European legislation.

Protocol and data collection.
After the initial surgical procedure with the construction of an intestinal stoma, patients were admitted to the ICU. By protocol, none of the patients received vasodilatory therapy or steroids before the first OPS images were obtained; hereafter such therapy was to the discretion of the attending physician, who was blinded for the OPS-imaging results. None of the patients received activated protein C during the protocol. Before baseline measurements, hypovolemia was excluded by repeated volume challenges up to the point where stroke volume (SV) did not increase any further, or when central venous pressure (CVP) reached 15 mm Hg. Mean arterial pressure (MAP) was maintained at a minimum level of 65 mm Hg with dopamine up to 15 μg/kg · min, in case peak flow velocity in the descending aorta was below 70 cm/s. In case peak flow velocity exceeded 70 cm/s, together with a MAP < 65 mm Hg, norepinephrine was added. Hereafter, routine macro-hemodynamic parameters. Cardiac index (CI), SV and peak flow velocity were measured by oesophageal Doppler technology (CardioQ®, Deltex Medical, West Sussex, UK) within ten minutes from the time of OPS imaging. Age, gender, length of stay (LOS), Acute Physiology And Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were documented (11,12). During the ICU stay sequential OPS imaging was performed on day 1 and day 3, with a lag time between sublingual and stoma region of less than 10 minutes.
**Imaging technique.**

The OPS technique, as described in detail elsewhere (2,13), consists of a hand-held device that illuminates an area of interest with polarized light, while imaging the remitted light through a second polarizer (analyser), oriented in a plane precisely orthogonal to the plane of illumination. If a wavelength within the haemoglobin absorption spectrum (e.g. 548 nm) is chosen, erythrocytes will appear dark and leukocytes may be visible as refringent bodies. The vessel walls itself are not visualized directly, although faint contours can be identified depending on the presence of intravascular erythrocytes.

**OPS imaging and analysis procedure.**

OPS imaging and semi-quantitative analysis, was performed as described in detail elsewhere (14). The inter-observer and intra-observer agreement for individual flow scores was validated both for microcirculatory networks and repeating vascular structures (14). In short, steady images of at least 20 seconds were obtained after gentle removal of saliva/faeces by an isotonic-saline-drenched gauze, avoiding pressure artefacts, and stored on digital videotape (SONY video walkman GV-D 1000E®, Sony, Tokyo, Japan). Intestinal stomas were penetrated with the OPS device 5-10 cm, beyond the abdominal wall. Subsequently, the images were captured in 5-10-second representative video clips in avi format (sonyDVgate®, Sony, Tokyo, Japan). Video clips were analyzed blindly by an investigator not involved in data collection and in random order to prevent coupling between images.

OPS images were obtained from three different regions within the site of interest and each image is divided into 4 equal quadrants. Quantification of flow (no flow: 0, intermittent flow: 1, sluggish flow: 2 and continuous flow: 3) is scored per quadrant, for each cohort of vessel diameter (small: 10-25 μm, medium 26-50 μm and large 51-100 μm), if applicable. The overall score, called microvascular flow index (MFI), is the sum of each quadrant-score, divided by the number of quadrants in which the vessel type is visible. The net result (MFI) is an average score over 12 quadrants (3 regions times 4 quadrants per region) derived from the overall flow impression of all vessels with a particular range of diameter in a given quadrant. Anatomically, microvascular beds of villi (small intestine) and crypts (colon) only consist of small vessels.

**Statistical analysis.**

Data are presented in medians and interquartile ranges (IQR). For comparison of groups non-parametrical tests are used; for comparison of two groups a Mann-Whitney test is applied and for comparison of more than 2 groups a Kruskal-Wallis test. Evolution over time was assessed by a non parametric test (Wilcoxon signed-rank test) for paired data. Non-parametric rank correlation is expressed as Spearman’s rho \( r \). A two-sided p value of < 0.05 is considered statistically significant.
Results

Patients, day 1.
Twenty-three ICU patients with a median APACHE II score of 20 (14-24) were enrolled in the study. All of them fulfilled the entry-criteria; cultures of the abdominal cavity revealed a mixed intestinal flora in all patients. Baseline characteristics and hemodynamic parameters are summarized in Table 1. ICU and in-hospital mortality was 26.1 and 34.7% respectively, with an ICU LOS of 15.3 (IQR 3-14.5) days and an in-hospital LOS of 29.8 (IQR 11.5-47) days. The first control group consisted of 19 healthy outpatient individuals with a median age of 59 (IQR 51-74) and a male:female ratio of 12:7; 9 patients had an ileostomy, 10 patients a colostomy. In the second control groups 10 non-sepsis patients with a less-than-24-hours-old intestinal stoma were included. Their median age was 61 (IQR 55-75) and their male:female ratio 6:4; 5 patients had an ileostomy, 5 patients a colostomy. It was possible to obtain good OPS images of both microvascular beds in all patients and no adverse events, such as bleeding or perforation of the stoma site, were reported. No re-operations for stoma necrosis or abdominal compartment syndrome had to be performed during the study.

Table 1. Characteristics study population day 1 (n = 23)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female, n</td>
<td>17/6</td>
</tr>
<tr>
<td>Age, years</td>
<td>70 (56-77)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20 (14-24)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7 (5-10)</td>
</tr>
<tr>
<td>Ventilator, use of, n</td>
<td>22</td>
</tr>
<tr>
<td>CVVH, use of, n</td>
<td>4</td>
</tr>
<tr>
<td>Norepinepherine, n (dose in μg/kg · min)</td>
<td>3; 0 (0-0)</td>
</tr>
<tr>
<td>Dopamine, n (dose in μg/kg · min)</td>
<td>23; 7 (4-14)</td>
</tr>
<tr>
<td>Stoma site</td>
<td></td>
</tr>
<tr>
<td>small intestine</td>
<td>5</td>
</tr>
<tr>
<td>colon</td>
<td>18</td>
</tr>
<tr>
<td>Surgical diagnosis, n</td>
<td></td>
</tr>
<tr>
<td>ischemia, vascular</td>
<td>1</td>
</tr>
<tr>
<td>ischemia, mechanical (strangulation)</td>
<td>4</td>
</tr>
<tr>
<td>blow out (carcinoma)</td>
<td>2</td>
</tr>
<tr>
<td>blow out (Ogilvie)</td>
<td>4</td>
</tr>
<tr>
<td>diverticulitis</td>
<td>6</td>
</tr>
<tr>
<td>anastomotic leakage</td>
<td>6</td>
</tr>
</tbody>
</table>

APACHE, acute physiology and chronic health evaluation; SOFA, sepsis-related organ failure assessment; CVVH, continuous veno venous hemofiltration. Data are presented as medians (25th-75th percentiles), unless stated otherwise.
Patients, day 3.

Twelve patients were evaluable; 7 were discharged and 2 died before day 3. Follow up was not available for 2 other patients. Evolution of systemic hemodynamic parameters, dosages of inotropic and vasopressor agents, lactate and pH, haemoglobin, PEEP settings and SOFA scores from day 1 to day 3 is shown in Table 2. Interestingly, three patients with persistent reduction in microcirculatory flow (sublingual MFI 1.92, 2.0 and 2.08 respectively) on day 3 survived to hospital discharge, whereas 2 patients with a normal flow (sublingual MFI 2.66 and 3.0 respectively) on day 3 died.

Table 2. Evolution over time of systemic hemodynamic parameters, PEEP settings and metabolic variables in the study population

<table>
<thead>
<tr>
<th></th>
<th>Day 1 (n=23)</th>
<th>Day 3 (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>97 (78-114)</td>
<td>98 (87-103)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>70 (66-87)</td>
<td>79 (68-90)</td>
<td>0.33</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>9 (7-14)</td>
<td>12 (9-16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiac index, L/min · m²</td>
<td>4.5 (3.5-5.1)</td>
<td>4.8 (3.6-6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dopamine dose, μg/kg · min</td>
<td>7 (4-14)</td>
<td>5 (2-8)</td>
<td>0.04</td>
</tr>
<tr>
<td>PEEP, cm H₂O</td>
<td>12 (8-14)</td>
<td>11 (10-15)</td>
<td>0.48</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>2.9 (1.4-5)</td>
<td>3.0 (2.1-3.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 (7.34-7.39)</td>
<td>7.38 (7.35-7.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Haemoglobin, mmol/L</td>
<td>5.2 (5-5.9)</td>
<td>5.3 (4.5-5.5)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

PEEP, positive end-expiratory pressure. Data are presented as medians (25th-75th percentiles). P values are calculated for paired data (n=12) by a non-parametric Wilcoxon signed-rank test.

Microcirculatory flow index day 1.

Intestinal stoma versus controls.

On day 1, MFI at the stoma site was significantly lower in the sepsis group (n = 23) as compared to the non-sepsis control group (n = 10) (median 2.08, IQR 1.25-2.42 and 3, IQR 3-3 respectively, p = 0.001). At the same time MFI at the stoma site of the non-sepsis group did not differ from the outpatient group (n = 19) (median 3, IQR 3-3 and 3, IQR 3-3 respectively, p = 0.29, fig.1).

Sublingual versus intestinal stoma.

On day 1, MFI of small vessels in the sublingual region did not show a significant correlation with MFI at the stoma site (r = 0.12, 95% CI -0.51-0.31, p = 0.59), in which, by anatomy, only vessels from the small type are present (fig. 2A).

Sublingual versus systemic hemodynamic parameters.

Correlation coefficients between MFI sublingual and macro-hemodynamic parameters such as heart rate (HR), CI, MAP, CVP, lactate and use of inotropic and vasopressors agents
were all insignificant (Table 3). All correlation coefficients between MFI sublingual site and parameters of morbidity (SOFA, LOS) were insignificant ($r_s = 0.27$ and $0.28$ respectively).

**Intestinal stoma versus systemic hemodynamic parameters.**

Similar non-significant correlation coefficients were found for MFI intestinal stoma and macro-hemodynamic parameters (Table 3), as well as for correlation coefficients between MFI intestinal stoma and parameters of morbidity (SOFA, LOS) ($r_s = 0.33$ and $-0.12$ respectively).

**Table 3.** Correlation between microvascular flow index and systemic hemodynamic parameters in study population, day 1 ($n = 23$)

<table>
<thead>
<tr>
<th></th>
<th>MFI sl</th>
<th>MFI stoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.004</td>
<td>-0.04</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.10</td>
<td>-0.08</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.07</td>
<td>-0.02</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>0.25</td>
<td>-0.32</td>
</tr>
<tr>
<td>Norepinephrine dose</td>
<td>0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>Dopamine dose</td>
<td>0.06</td>
<td>-0.21</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.04</td>
<td>-0.23</td>
</tr>
<tr>
<td>MFI sublingual</td>
<td>-</td>
<td>0.12</td>
</tr>
<tr>
<td>MFI intestinal stoma</td>
<td>0.12</td>
<td>-</td>
</tr>
</tbody>
</table>

MFI, microvascular flow index (small vessels; < 20 μm); sl, sublingual. Data are presented as Spearman rank correlation ($r_s$).

**Figure 1.** Boxplot of microvascular flow index (MFI) of small vessels (< 20 μm) at the intestinal stoma site of the outpatient group, non-sepsis group (day 1) and sepsis group day 1. * $p < 0.05$. 
Microcirculatory flow index day 3.

Intestinal stoma in relation to day 1.
Intestinal stoma MFI increased from day 1 to day 3 significantly (median 1.83, IQR 1.33-2.46 and 2.66, IQR 2.34-2.83 respectively, p = 0.02) (fig. 3).

Sublingual in relation to day 1.
In comparison to day 1, sublingual MFI on day 3 also increased significantly (median 2.08, IQR 1.25-2.42 and 2.66, IQR 2.5-2.92 respectively, p = 0.01 (fig.3). MFI-changes over time from day 1 to day 3 for individuals are depicted in fig. 2C.

Sublingual versus intestinal stoma.
In contrast to the situation on day 1, there was a significant correlation between MFI of the stoma and sublingual region ($r_s = 0.74$, 95% CI 0.28-0.92, p = 0.006) (fig.2B, Table 4) on day 3.

Sublingual versus systemic hemodynamic parameters.
On day 3 MFI sublingual showed a significant correlation with CI ($r_s = 0.65$, p < 0.05), whereas correlations with HR, MAP, CVP, lactate and use of inotropic and vasopressors agents remained insignificant (Table 4). Correlation coefficients between MFI sublingual and parameters of morbidity (SOFA, LOS) were insignificant ($r_s = 0.28$ and -0.26 respectively).

Intestinal stoma versus systemic hemodynamic parameters.
On day 3 MFI stoma showed a significant correlation with HR ($r_s = 0.79$, p < 0.01). Correlations with CI, MAP, CVP, lactate and use of inotropic and vasopressors agents remained insignificant (Table 4). Correlation coefficients between MFI intestinal stoma and parameters of morbidity (SOFA, LOS) were insignificant ($r_s = -0.13$ and -0.46 respectively).

Table 4. Correlation between microvascular flow index and systemic hemodynamic parameters in study population, day 3 (n = 12).

<table>
<thead>
<tr>
<th></th>
<th>MFI sl</th>
<th>MFI stoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.57</td>
<td>0.79**</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.65*</td>
<td>0.51</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>-0.37</td>
<td>-0.37</td>
</tr>
<tr>
<td>Norepinephrine dose</td>
<td>0.13</td>
<td>0.36</td>
</tr>
<tr>
<td>Dopamine dose</td>
<td>0.46</td>
<td>0.13</td>
</tr>
<tr>
<td>Lactate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MFI sublingual</td>
<td>-0.74**</td>
<td>-</td>
</tr>
<tr>
<td>MFI intestinal stoma</td>
<td>-0.74**</td>
<td>-</td>
</tr>
</tbody>
</table>

MFI, microvascular flow index (small vessels; < 20 μm); sl, sublingual; NA, not available. Data are presented as Spearman rank correlation ($r_s$). ** $p < 0.01$, * $p < 0.05$
Figure 2. Scatter of microvascular flow index (MFI) of small vessels (< 20 μm) in the sublingual region versus the MFI in the intestinal stoma region. On day 1 each individual is represented by a circle (○ colostomy, ● ileostomy); $r$, day 1 = 0.12 (Fig.2A). On day 3 individuals are represented by a triangle (▲); $r$, day 3 = 0.74 (Fig.2B). Arrows depict the movement over time from MFI day 1 to day 3 for each individual in relation to the identity line (−−−) (Fig.2C).
Discussion

The results in the presented study are consistent with the hypothesis that microcirculatory abnormalities rather than systemic hemodynamic parameters are the predominant factor during sepsis and septic shock (15,16). In accordance with earlier reports (3,17), we could not find a significant correlation on day 1 between the commonly used systemic hemodynamic parameters (HR, MAP CVP and CI) on the one hand, and abnormalities in microcirculatory blood flow, as established with OPS imaging, on the other hand. A recent report about the effect of dobutamine in septic shock on microcirculatory alterations, independent of systemic hemodynamic changes (18) seems to be in accordance with our presented data.

On day 3 the correlation between microcirculatory blood flow and systemic hemodynamics seems, in part, to be restored. Whether this is an true effect due to the evolution over time of sepsis itself, or a net result of a complex of therapeutic interventions, remains to be established.

The most downstream ‘hemodynamic compartment’ consists of microcirculatory units. During sepsis, heterogeneity of flow between and within these microcirculatory units seems to be a characteristic finding, thus creating the concept of microcirculatory weak units (15). In this study, at a specific time point day 1, no correlation between the microvascular flow of two different microvascular beds (sublingual and intestinal region) could be established. In other words: if one looks at OPS images of the sublingual microvascular bed during sepsis, it is impossible to predict what these images will be at the same time in an
Relationship between sublingual and intestinal microcirculation in sepsis

The complete absence of correlation on day 1 between hemodynamic parameters of systemic and microcirculatory compartments, as well as between equal types of compartments, enhances the idea of a dispersive nature of flow during the initial phase of sepsis. A combination of local microcirculatory factors, such as activated coagulation, shedding of the glycocalyx during endothelial cell activation (19), reduced red blood cell deformability (9), iNOS expression (20) and loss of autoregulation (8) is likely to influence microcirculatory flow, rather than systemic hemodynamic parameters.

On day 3 this dispersive nature of microcirculatory flow has ceased and a correlation between MFI sublingual and intestinal stoma could be established, mainly by an overall movement of MFI in both regions towards normal values around the identity line (fig. 2).

Once again the evolvement over time of sepsis itself and influences of therapeutic strategies may play a role, as expressed in the model of microcirculatory and mitochondrial distress syndrome (MMDS) (16). It seems therefore important to take these time dependent relations into account by the design of further sepsis studies.

Time-dependency might explain why, in contrast to our present data, an earlier pilot study reported a correlation between microvascular flow in stomas and the sublingual region (21). In this study of Spronk et al. time of inclusion was not defined and almost all patients were included after the first 24 hours of sepsis, thus potentially eliminating the initial dispersion of flow in both microcirculatory beds.

Recently, others demonstrated a good correlation between sublingual microcirculatory perfusion and gastric mucosal PCO₂ (6,22), suggesting a good correlation between sublingual/buccal and gastric perfusion. However, in human studies no direct observations of the stomach microcirculation are made and in the animal study of Fries et al. direct microcirculatory OPS observations are made of the serosa of the stomach as opposed to the mucosa of the small and large intestine in this study. Furthermore, like in all animal cecal-ligation-and-puncture sepsis-models, observations were made a few hours before death. The possibility that such terminal model of sepsis could lead to a final common pathway of microcirculatory failure, and therefore to a correlation between different microcirculatory beds, cannot be ruled out.

It is of note that in this study all 3 patients with persistent reduction in microcirculatory flow (sublingual MFI 1.92, 2.0 and 2.08 respectively) on day 3 survived to hospital discharge, whereas 2 out of 9 patients with a normal flow (sublingual MFI 2.66 and 3.0 respectively) on day 3 died. However, this observational study was not designed to detect differences between survivors and non-survivors. To address the issue of relation between microcirculatory alterations and parameters of morbidity and mortality, Sakr et al. (7) performed a study, in which was demonstrated that persistence of microcirculatory alterations during sepsis was associated with organ dysfunction and non-survival. In a paper of De Backer and co-workers the proportion of perfused small vessels was higher in survivors than in non-survivors, but there was no correlation between microcirculatory alterations and MAP, CI and mixed-venous oxygen saturation (3).
With regard to the use of OPS imaging in intestinal stomas, as a model of intestinal microcirculation, several limitations of the study have to be taken into account. Since the surgical procedure itself might influence the microcirculation of the intestinal mucosa, we included a second control group of non-sepsis patients with a newly constructed stoma. MFI of this non-sepsis group differed significantly from the sepsis group during the initial phase of the abdominal sepsis (fig.1), whereas comparison of MFI between the non-sepsis group and the outpatient group showed no differences. Typical heterogeneity of flow only was observed during sepsis, both in the sublingual and intestinal microvascular beds and was absent in both control groups. This suggests that sepsis, and not the surgical procedure, is the main determinant for the observed microcirculatory flow alterations.

A second confounding factor on intestinal stoma microcirculation could have been the influence of the intra-abdominal pressure. Routine measurement of intra-abdominal pressure was not part of the protocol, but only performed in case of clinical suspicion of an abdominal compartment syndrome. However, none of the patients underwent a relaparotomy to relieve abdominal pressure during the protocol and an expected left-shift of the relation between MFI stoma and MFI sublingual (since elevated intra-abdominal pressure would theoretically diminish only intestinal flow and not sublingual flow) (fig.2) was not observed.

Thirdly, not only the influence of local inflammation with concomitant vasoconstriction and vasodilation as a result of generalized peritonitis might have been of influence, but it is also well known that the release of systemic pro- and anti-inflammatory mediators differs strongly between the various sepsis models (23). Furthermore, variation in local iNOS expression may influence microcirculatory blood flow (20).

Finally, the approach used, to score microcirculatory flow in a semi-quantitative way has its limitations. Although the method was specifically designed to differentiate between heterogeneous flow patterns during sepsis, it is still possible to underscore subtle microcirculatory abnormalities of individual vessels, since the score is derived from an overall impression of a specific vessel type in a particular quadrant. Using other scores or direct measurement of flow in each individual vessel may have yielded different results.

**Conclusions**

In conclusion, no correlation between the microvascular flow in the sublingual region and the mucosa of an intestinal stoma could be found during day 1 of an abdominal sepsis in humans. Together with the absence of correlation between systemic hemodynamic parameters and microcirculatory flow, these data suggest a complete dispersion of blood flow in the different hemodynamic compartments during abdominal sepsis. The observed microcirculatory abnormalities during sepsis in an intestinal stoma seem to be determined by the sepsis itself, rather than by the surgical procedure. On day 3 however, correlation
between sublingual and intestinal microcirculatory flow appears to be restored, mainly due to a normalization of flow in both regions. It seems important to take this time-related dispersion between different microcirculatory beds into account for the design of future sepsis studies and to extend the research on correlation between sublingual and intestinal microcirculatory abnormalities to other human models of sepsis.

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References


