A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Sublingual microcirculatory changes during high-volume hemofiltration in hyperdynamic septic shock patients

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Abstract

Introduction
Previous studies have suggested that high volume hemofiltration (HVHF) may contribute to revert hypotension in severe hyperdynamic septic shock patients. However, arterial pressure stabilization occurs due to an increase in systemic vascular resistance, which could eventually compromise microcirculatory blood flow and perfusion. The goal of this study was to determine if HVHF deteriorates sublingual microcirculation in severe hyperdynamic septic shock patients.

Methods
This was a prospective, nonrandomized study at a 16-bed, medical-surgical intensive care unit of a university hospital. We included 12 severe hyperdynamic septic shock patients (norepinephrine requirements > 0.3 μg/kg/min and cardiac index > 3.0 L/min/m²) who underwent a 12-hour HVHF as a rescue therapy according to a predefined algorithm. Sublingual microcirculation (Microscan * for NTSC, Microvision Medical), systemic hemodynamics and perfusion parameters were assessed at baseline, at 12 hours of HVHF, and 6 hours after stopping HVHF.

Results
Microcirculatory flow index increased after 12 hours of HVHF and this increase persisted 6 hours after stopping HVHF. A similar trend was observed for the proportion of perfused microvessels. The increase in microcirculatory blood flow was inversely correlated with baseline levels. There was no significant change in microvascular density or heterogeneity during or after HVHF. Mean arterial pressure, and systemic vascular resistance increased while lactate levels decreased after the 12-hour HVHF.

Conclusions
The use of HVHF as a rescue therapy in patients with severe hyperdynamic septic shock does not deteriorate sublingual microcirculatory blood flow despite the increase in systemic vascular resistance.
**Introduction**

High volume hemofiltration (HVHF) is a potential rescue therapy in severe septic shock patients, and some clinical studies suggest that HVHF can decrease vasopressor requirements and improve lactate clearance [1, 2]. Therefore, HVHF may have a place in refractory septic shock by contributing to stabilize systemic hemodynamics and eventually improving systemic perfusion.

However, studies supporting HVHF are rather small and non-randomized, which precludes making more definitive conclusions about its real impact on clinically relevant outcomes. Indeed, decreases in vasopressor requirements and lactate levels may not necessarily reflect a real improvement in perfusion. In the past, therapies such as steroids and nitric oxide synthase inhibitors have shown to increase vascular tone without any significant benefit in terms of perfusion or survival [3, 4]. In addition, it is now well accepted that hyperlactatemia may be explained by mechanisms not related to hypoperfusion [5]. Clearly, it would be desirable to assess the impact of HVHF on perfusion determinants, and particularly on microcirculation, more directly.

Development of optical techniques such as orthogonal polarized spectral imaging, and more recently, side dark field videomicroscopy (SDF), has made it possible to visualize microcirculation at bedside. Microcirculation is known to be markedly compromised during septic shock and these disturbances are considered to play a central role in multiple organ failure. By using these novel techniques the impact of conventional therapies on microcirculation is starting to be unraveled [6-9].

There is very limited information concerning the potential effects of HVHF on microcirculation during septic shock. Only one previous experimental study has addressed this subject [10], but unfortunately, the model induced only non-severe microcirculatory derangements, which makes the results difficult to interpret. Beneficial effects of HVHF have been related to non-specific removal of mediators, which could potentially contribute to revert microcirculatory disturbances induced by sepsis. However, the most evident clinical effect of HVHF is an increase in arterial pressure, which occurs as result of an increased systemic vascular resistance, and not to an increase in cardiac output, at least in hyperdynamic patients [2]. Therefore, it is critical to discard that this increase in vascular resistance is not associated to a detrimental effect on microcirculatory flow.

We performed a prospective observational pilot study to assess changes in sublingual microcirculation during HVHF in severe hyperdynamic septic shock patients.

**Methods**

Our local ethics committee approved the study and informed consent was obtained from the patients or their relatives. All septic shock patients in our institution are managed with a norepinephrine-based, perfusion-oriented, management algorithm. In this algorithm,
nepinephrine dose is adjusted at least once every hour to keep MAP $\geq 65$ mmHg (or more frequently if MAP $< 60$ or $> 85$ mmHg). Dobutamine is indicated as an inotrope for patients with low cardiac index (Cl) ($< 2.5$ L/min/m$^2$), or low central venous oxygen saturation ($\text{ScvO}_2$) or mixed venous oxygen saturation ($\text{SmvO}_2$) values ($< 60\%)$ not responsive to other measures and with a mean arterial pressure (MAP) $> 65$ mmHg. The characteristics of this algorithm have been published elsewhere [2, 11], and it includes HVHF as a rescue therapy. HVHF was indicated to patients who failed to respond to all preceding management steps including source control and fluid optimization guided by pulse pressure variation ($\Delta PP$). Specific inclusion criteria for this study were: septic shock according to the 1992 ACCP-SCCM consensus [12], norepinephrine requirements $> 0.3$ μg/kg/min to maintain MAP $> 65$ mmHg for at least one hour before deciding HVHF, progressive hyperlactatemia ($> 2.4$ mmol/l and an increase in lactate levels during 6 hours of full resuscitation), and a Cl $> 3$ L/min/m$^2$. Patients without full commitment for resuscitation, or with active bleeding or an undrained source of surgical sepsis were excluded.

All patients had a pulmonary artery catheter in place, and were mechanically ventilated following current guidelines [13], with fentanyl/midazolam sedation targeted to a SAS score <3. No patient received steroids, vasopressin or drotrecogin alpha either previously or during the hemofiltration procedure. Blood transfusions were indicated before the procedure if a hemoglobin value $< 8$ gr/dl.

**High volume hemofiltration technique**

A 13.5 French double lumen hemodialysis catheter was inserted in the femoral vein under local anesthesia (Q-plus, Covidien, Mansfield, MA, USA). HVHF was performed with a polysulfone hemofilter, 1.5 m$^2$ of area, wall thickness 40μm and internal diameter 200μm (Diacap acute-M, BBraun, Melsungen, Germany). Hemofiltration monitor was adjusted for a blood flow of 200 ml/min. Ultrafiltration rate was increased gradually during the first 60 min according to hemodynamic tolerance up to 100 ml/kg/h keeping always a neutral fluid balance (Diapac, BBraun, Melsungen, Germany). Pre-hemofilter ultrafiltrate reposition was performed using a bicarbonate based solution with the following final composition: sodium 140.0 mmol/L, potassium 2.0 mmol/L, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, chloride 111 mmol/L, bicarbonate 35 mmol/L, dextrose 1 g/L and osmolality 296 mOsm/L (S-BIC 35 and SH-EL 02, BBraun, Avitum AG, Glandorf, Germany). The extracorporeal system was not anticoagulated and patient core temperature was kept over 35°C by the heating device coupled to the monitor and by warming the solutions when necessary. According to our ICU protocol [2], all patients were scheduled to receive a 12-hour period of HVHF with a single hemofilter, during which additional fluids and norepinephrine dose were adjusted to maintain MAP $\geq 65$ mmHg and a $\Delta PP < 10\%$. Before starting the procedure all patients should have a $\Delta PP < 10\%$ which was calculated as $\Delta PP = 100 \times (PP\ max - PP\ min)/[(PP\ max - PP\ min)/2]$. 


Measurements
Patients were assessed before starting HVHF (baseline), after 12 hours of HVHF, and 6 hours after stopping HVHF. Each assessment consisted in hemodynamic measurements: MAP, heart rate, CI, pulmonary artery occlusion pressure, central venous pressure; vasoactive requirements; perfusion parameters: arterial lactate, SmvO₂, urine output; score of organ failure assessment (SOFA); and sublingual microcirculation imaging.

Sublingual microcirculation imaging
Sublingual microcirculation was assessed with SDF with a 5x lens (Microscan® for NTSC, Microvision Medical). At each time-point, at least five 10-20 sec images were recorded. After gently removing saliva and oral secretions the probe was applied over the mucosa at the base of the tongue. Special care was taken to avoid exerting excessive pressure on the mucosa, which was verified by checking ongoing flow in the larger microvessels (>50 μm). Analog images were digitalized by using the pass-through function of a digital video camera recorder (Sony DCR-HC96, for NTSC) and were recorded instantaneously to AVI format in a personal computer with the aid of a commercial software (DVGate Plus 2.3, Sony Corporation).

Images were analyzed blindly and randomly using a semiquantitative method. According to recommendations of a consensus committee [14], the image analysis consisted in determinations of (i) flow: proportion of perfused vessels (PPV) and microvascular flow index (MFI), (ii) density: total vascular density (TVD) and perfused vascular density (PVD), and (iii) heterogeneity: MFI heterogeneity (Het MFI). Briefly, to determine MFI, the image was divided in four quadrants and the predominant type of flow was assessed in each quadrant and characterized as absent=0, intermittent=1, sluggish=2 or normal=3; the values of the 4 quadrants were averaged. MFI heterogeneity was calculated as Het MFI = (MFI_max – MFI_min) x 100 / MFI_mean. For TVD and PVD a gridline consisting of 3 horizontal and 3 vertical equidistant lines was superimposed on the image. All the vessels crossing the lines were counted and classified as perfused (continuous flow) and non-perfused vessels (absent or intermittent flow, this is at least 50% of time with no flow). Densities were calculated as the total number of vessels (TVD), or the number of perfused vessels (PVD), divided by the total length of the gridline in millimeters. PPV was calculated as PVD x 100 / TVD (%). Large and small vessels (< 20μm) were analyzed separately. According to recommendations from experts [14], the analysis of large vessels are of limited interest and in this study they were used as a quality control to ensure that no excessive pressure was being applied on the sublingual mucosa. Therefore, all the data from sublingual microcirculation presented correspond to small vessels.

Clinical follow-up
Patients were classified as responders to a 12-hour HVHF session if a 30% decrease in norepinephrine requirements and lactate levels could be demonstrated. Clinical follow-up was until day 28.
Statistical analysis

Data with normal distribution are presented as mean ± standard deviation, and data not normally distributed as median and 25th-75th percentiles. Repeated measures analysis of variance (ANOVA) with Bonferroni post hoc test, was used to evaluate changes along time for normally distributed data, and Friedman test with Dunn test correction was used for variables without normal distribution. Correlations were determined by the Pearson coefficient or Spearman’s rho, for data with normal and not normal distribution respectively. Analysis was performed with GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California, USA). A two-sided p < 0.05 was considered statistically significant.

Results

Twelve consecutive severe hyperdynamic septic shock patients, 7 men and 5 women, age 57.9 ± 13.2 years old, were recruited between March 2007 and March 2009. Baseline characteristics are presented in Table 1. The more common sources were abdominal in 5 and pulmonary in 2. All patients started HVHF within less than 6 hours since meeting the inclusion criteria. One patient had a baseline norepinephrine requirement of 0.28 μg/kg/min but in the previous hours he had already met inclusion criteria including norepinephrine requirement > 0.3 μg/kg/min for more than one hour with a ΔPP < 10%. Baseline values were measured just before starting HVHF. Only two patients were receiving dobutamine for at least 2 hours before starting HVHF and its dose was not changed during the procedure (patients 1 and 6). All patients survived throughout the study period but five patients had died at day 28 (42%). No technical problems with the procedure were observed and no change of hemofilter was required in any patient.

Hemodynamic and perfusion parameters

MAP and systemic vascular resistance index (SVRI) increased and lactate levels decreased at 12 hours of HVHF, with no changes thereafter. CI, SmvO₂, O₂ transport and O₂ consumption did not change during or after HVHF (Table 2).

Microcirculatory parameters

Density scores (TVD and PVD), and Het Index MFI didn’t show any significant variation during the study (Figure 1 and Table 2). MFI significantly increased compared to baseline after 12 hours of HVHF, without deterioration after HVHF was stopped. In parallel, there was a trend to increased PPV during HVHF (Figure 2 and Table 2). Interestingly, 3 of the 4 patients with the worst MFI (< 2) had a notorious improvement after 12 hours of HVHF.

We looked for correlations between microcirculation at baseline and the relative changes occurring during the 12-hour HVHF. For PVD and PPV there was a strong negative correlation such that patients with the worst scores at baseline had the largest improvements during the 12-hour HVHF (Figure 3). For TVD, MFI and Het MFI there was no significant correlation between baseline values and their relative changes during
In addition, there was no significant correlation between microcirculatory changes and changes in hemodynamic and perfusion parameters.

**Discussion**

In the present study performed in severe hyperdynamic septic shock patients we found no deterioration of sublingual microcirculation during HVHF despite an increase in systemic vascular resistance. Furthermore, microcirculatory flow index significantly improved during HVHF while PPV showed the same trend although not reaching a statistical significance. These effects seem to be more marked in patients with more impaired basal microcirculation.

Several experimental and clinical studies have suggested that HVHF can be an effective rescue therapy in refractory septic shock, stabilizing hemodynamics, decreasing vasopressor requirements, and improving lactate clearance [1, 2, 15]. This is the first study that explores the effects of HVHF on microcirculation in septic shock patients. We observed an increase

### Table 8.1 Baseline characteristics of the patients at the moment of starting HVHF.

<table>
<thead>
<tr>
<th>Patient N°</th>
<th>Diagnosis</th>
<th>APACHE II</th>
<th>SOFA</th>
<th>Survival (day 28)</th>
<th>MAP (mmHg)</th>
<th>NE (μg/kg/min)</th>
<th>CI (L/min/m²)</th>
<th>SmvO₂ (%)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cholangitis</td>
<td>34</td>
<td>13</td>
<td>yes</td>
<td>70</td>
<td>0.30</td>
<td>3</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Necrotizing fascitis</td>
<td>24</td>
<td>10</td>
<td>yes</td>
<td>67</td>
<td>0.56</td>
<td>5.5</td>
<td>79</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>Cholangitis</td>
<td>25</td>
<td>11</td>
<td>yes</td>
<td>65</td>
<td>0.50</td>
<td>5.3</td>
<td>76</td>
<td>8.3</td>
</tr>
<tr>
<td>4</td>
<td>Catheter related sepsis</td>
<td>31</td>
<td>15</td>
<td>no</td>
<td>70</td>
<td>0.60</td>
<td>3.1</td>
<td>71</td>
<td>4.1</td>
</tr>
<tr>
<td>5</td>
<td>Diverticulitis</td>
<td>19</td>
<td>14</td>
<td>yes</td>
<td>75</td>
<td>0.37</td>
<td>5.5</td>
<td>80</td>
<td>2.6</td>
</tr>
<tr>
<td>6</td>
<td>Peritonitis</td>
<td>19</td>
<td>11</td>
<td>no</td>
<td>64</td>
<td>0.30</td>
<td>4.4</td>
<td>61</td>
<td>6.7</td>
</tr>
<tr>
<td>7</td>
<td>Pneumonia</td>
<td>21</td>
<td>13</td>
<td>yes</td>
<td>74</td>
<td>0.50</td>
<td>3.1</td>
<td>58</td>
<td>2.6</td>
</tr>
<tr>
<td>8</td>
<td>Necrotizing fascitis</td>
<td>25</td>
<td>13</td>
<td>no</td>
<td>64</td>
<td>1.00</td>
<td>4.8</td>
<td>79</td>
<td>4.5</td>
</tr>
<tr>
<td>9</td>
<td>Pyonephrosis</td>
<td>23</td>
<td>13</td>
<td>yes</td>
<td>66</td>
<td>0.28</td>
<td>3.5</td>
<td>71</td>
<td>3.6</td>
</tr>
<tr>
<td>10</td>
<td>Mesenteric ischemia</td>
<td>23</td>
<td>13</td>
<td>yes</td>
<td>62</td>
<td>0.62</td>
<td>3.4</td>
<td>78</td>
<td>2.6</td>
</tr>
<tr>
<td>11</td>
<td>Empyema</td>
<td>27</td>
<td>14</td>
<td>no</td>
<td>63</td>
<td>0.30</td>
<td>4.8</td>
<td>96</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>Endocarditis</td>
<td>25</td>
<td>15</td>
<td>no</td>
<td>70</td>
<td>0.60</td>
<td>3</td>
<td>70</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td><strong>24.7</strong></td>
<td><strong>12.8</strong></td>
<td><strong>67.5</strong></td>
<td><strong>0.49</strong></td>
<td><strong>4.1</strong></td>
<td><strong>72</strong></td>
<td><strong>5.4</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td></td>
<td><strong>4.4</strong></td>
<td><strong>1.7</strong></td>
<td></td>
<td><strong>4.3</strong></td>
<td><strong>0.21</strong></td>
<td><strong>1.0</strong></td>
<td><strong>11</strong></td>
<td><strong>3.0</strong></td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II (Acute Physiology and Chronic Health Evaluation II), CI (cardiac index), MAP (mean arterial pressure), NE (norepinephrine dose), PAOP (pulmonary arterial occlusion pressure), SmvO₂ (mixed venous oxygen saturation), SD (standard deviation)
in sublingual microcirculatory blood flow during HVHF. Interestingly, this increase occurred despite an increase in SVR and a trend to decreased cardiac output. One of the theories proposed to explain microcirculatory alterations in sepsis is the presence of shunt. The observation of increasing microcirculatory blood flow paralleled by increasing vascular resistance and decreasing cardiac output may be explained by a reversal of shunt.

The underlying mechanisms involved in the changes observed on hemodynamics and microcirculation are unclear. HVHF may remove some inflammatory mediators involved in the hemodynamic collapse of refractory septic shock from the blood compartment or the extravascular space [16]. Due to its broad theoretical physiologic effects, HVHF could potentially influence several microcirculatory parameters and improve microcirculatory derangements in septic shock. However, because of the uncontrolled design of our study we can’t rule out that the changes observed on hemodynamics and microcirculation were not

### Table 8.2 Evolution of microcirculatory scores, hemodynamic and perfusion parameters during the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>HVHF 12 hours</th>
<th>6 hours after HVHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>67.5 ± 4.3</td>
<td>74.5 ± 6.8 b</td>
<td>76.0 ± 9.4 b</td>
</tr>
<tr>
<td>NE (μg/kg/min)</td>
<td>0.49 ± 0.21</td>
<td>0.44 ± 0.45</td>
<td>0.26 ± 0.38</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>4.06 ± 1.11</td>
<td>3.68 ± 1.36</td>
<td>3.55 ± 1.12</td>
</tr>
<tr>
<td>SmvO₂ (%)</td>
<td>72.4 ± 1.7</td>
<td>71.4 ± 7.0</td>
<td>76.1 ± 6.0</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>5.38 ± 2.99</td>
<td>3.66 ± 2.39 b</td>
<td>3.64 ± 3.89 b</td>
</tr>
<tr>
<td>IDO₂ (mL/min/m²)</td>
<td>543 ± 211</td>
<td>483 ± 350</td>
<td>475 ± 173</td>
</tr>
<tr>
<td>IV0₂ (mL/min/m²)</td>
<td>137 ± 63</td>
<td>135 ± 101</td>
<td>108 ± 40</td>
</tr>
<tr>
<td>O₂ER (%)</td>
<td>26 ± 12.3</td>
<td>27.8 ± 0.7</td>
<td>23.1 ± 6.0</td>
</tr>
<tr>
<td>SVRI (dyne·s·cm⁻⁵·m⁻²)</td>
<td>1027 ± 268</td>
<td>1373 ± 408 a</td>
<td>1432 ± 375 a</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>38.1 ± 1</td>
<td>37.2 ± 0.9</td>
<td>37.5 ± 1.1</td>
</tr>
<tr>
<td>SOFA</td>
<td>12.8 ± 1.7</td>
<td>13.1 ± 2.1</td>
<td>12.4 ± 2.5</td>
</tr>
<tr>
<td>TVD (n/mm)</td>
<td>13.1 ± 1.9</td>
<td>13.6 ± 3.3</td>
<td>14.2 ± 3.8</td>
</tr>
<tr>
<td>PVD (n/mm)</td>
<td>9.6 ± 2.5</td>
<td>11.1 ± 3.0</td>
<td>12.1 ± 4.3</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>73.6 ± 15.6</td>
<td>81.7 ± 13.3 c</td>
<td>83.2 ± 14.7 c</td>
</tr>
<tr>
<td>MFI *</td>
<td>2.15 (1.64 - 2.28)</td>
<td>2.5 (1.96 - 2.7) a</td>
<td>2.5 (2.31 - 2.63) a</td>
</tr>
<tr>
<td>Het Index MFI *</td>
<td>0.44 (0.36 - 0.47)</td>
<td>0.4 (0.12 - 0.65)</td>
<td>0.29 (0.18 - 0.32)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, or median and 25th-75th percentiles (*). p < 0.01 versus baseline, b p < 0.05 versus baseline, c p < 0.06 versus baseline.

Abbreviations: CI (cardiac index), Het Index MFI (MFI Heterogeneity index), IDO₂ (Oxygen delivery index), IV0₂ (Oxygen consumption index), MAP (mean arterial pressure), MFI (microvascular flow index), NE (norepinephrine), O₂ER (Oxygen extraction ratio), PPV (proportion of perfused vessels), PVD (perfused vascular density), Smvo₂ (mixed venous oxygen saturation), SOFA (Sequential Organ Failure Assessment), SVRI (systemic vascular resistance index), TVD (total vascular density).
related to HVHF. They might correspond to the natural evolution of septic shock after initial resuscitation, as shown by Sakr et al. [17], or occur as the result of other co-interventions such as ongoing fluids or a strict hemodynamic management. Despite this caveats we still believe HVHF was responsible for the improvements observed on hemodynamics and microcirculation. Supporting this idea, changes occurred during the 12 hours of HVHF but not during the 6 hours that followed HVHF interruption.

Although norepinephrine was always titrated to keep a MAP ≥ 65 mmHg average MAP increased from 67.5 at baseline, to 74.5 mmHg at 12 hours of HVHF. This increase in MAP occurred because most patients exhibited a persistent trend to increase MAP during HVHF and norepinephrine was usually adjusted only once per hour. Theoretically MAP could influence microcirculatory blood flow but we found no significant correlation between changes in MAP and changes in MFI during the 12 hour HVHF. In addition, we considered the possibility that the trend to decreased doses of norepinephrine might have influenced the

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**Figure 8.1** Effects of HVHF on sublingual microvascular density. The graphs present the individual evolution of total vascular density (TVD, upper graph) and perfused vascular density (PVD, lower graph) of small vessels (< 20 μm) at baseline, at the end of the 12-hour period of HVHF, and 6 hours after stopping HVHF. Density is expressed as number of vessels / total length of the gridline in millimeters. There was no significant change.
change in MFI but again we found no correlation between changes in norepinephrine and changes in MFI. Against a role for arterial pressure and vasopressors, two nice studies have shown that changes in arterial pressure induced by changing norepinephrine doses did not influence sublingual MFI across a large range of MAP and norepinephrine doses [18, 19].

A previous elegant experimental study compared the effects of standard hemofiltration versus HVHF in a porcine model of hyperdynamic sepsis [10]. Although HVHF was associated with an improvement in global hemodynamics, no beneficial effect on microcirculatory flow, hepatosplanchnic hemodynamics, cellular energetics, endothelial injury or systemic inflammation, could be observed. Unfortunately, the model induced only mild to moderate disturbances in hemodynamics and microcirculatory flow and therefore, it did not represent a severe septic shock condition.

Until now, only a few uncontrolled small studies have evaluated the hemodynamic effects of HVHF in septic shock patients. Honore et al., showed that HVHF-responders improved cardiac output and systemic hemodynamics in a series of hypodynamic septic shock patients[1]. In our previous report involving only hyperdynamic septic shock

![Figure 8.2 Effects of HVHF on sublingual microvascular flow. The graphs present the individual evolution of flow assessed by the percent of perfused vessels (PPV, upper graph) and by the microvascular flow index (MFI, lower graph) of small vessels (< 20 μm) at baseline, at the end of the 12-hour period of HVHF, and 6 hours after stopping HVHF. * p < 0.05 compared to baseline.](image)
patients [2], we found that MAP increased mainly due to an increase in SVRI. However, an improvement in MAP at the expense of an increase in SVRI may not necessarily be beneficial in terms of microcirculatory flow [19], perfusion parameters [20], or survival [4]. The nonselective nitric oxide synthase inhibitor 546C88 induced a strong pressor effect in septic shock patients, but unfortunately this effect was associated with a higher incidence of pulmonary hypertension, systemic arterial hypertension and heart failure, a decreased cardiac output, and a higher mortality [4]. Therefore, our results may be relevant since they suggest that the potential beneficial hemodynamic effect of HVHF is not at expense of microcirculatory flow.

It is rather surprising that only 4 of 12 patients exhibiting a severe septic shock presented a low MFI < 2. This observation is consistent with recent data from Dubin et al. [18], and Jhanji et al. [19], who found a mean basal MFI of 2.1 ± 0.7 and 2.3 ± 0.4, respectively. In fact, in the first study, only 4 of 22 septic shock patients exhibited a MFI < 2. This is in sharp contrast with the data of Treziak et al. [21] who reported MFI values < 1.5 early after emergency room or ICU admission. It appears that MFI values, resembling what happens

Figure 8.3 Relationship between baseline sublingual microcirculatory parameters and their change during the 12-hour HVHF. The upper graph shows a significant correlation between baseline values of perfused vascular density (PVD) and their variation during the 12-hour HVHF. The lower graph shows a similar correlation between the baseline values of the percent of perfused vessels (PPV) and their variation during the 12-hour HVHF. Both PVD and PPV were calculated for small vessels (< 20 um).
with $\text{ScvO}_2$, are very low in pre-resuscitated patients but may improve after aggressive resuscitation, except in refractory dying patients.

We found a negative correlation between the severity of basal microcirculatory derangements and their change after a 12-hour HVHF session. Similar observations have been reported by other authors when studying the effect of different interventions on microcirculatory dysfunction in septic patients. Dubin et al. assessed the effects of increasing MAP over microcirculatory dysfunction and found that changes in perfused capillary density correlate inversely with basal values [18]. Sakr et al. showed that changes in capillary perfusion after red blood cell transfusion correlate negatively with baseline capillary perfusion [17]. At this moment we have no clear explanation for these findings.

The present study has several limitations. First, it includes a small number of patients. In our current septic shock management algorithm, HVHF is a rescue therapy. As reported elsewhere [11], the strict application of our protocol has lead to an improvement in outcome, and therefore only 20% of septic shock patients are eligible for this intervention. Since only hyperdynamic septic shock patients with norepinephrine requirements > 0.3 μg/kg/min and progressive hyperlactatemia were included in this study, we recruited only 1 patient every 45 days. This fact precluded the inclusion of a larger number of patients. Second, we did not include a control group. This limitation is shared by several studies addressing the impact of conventional therapies on microcirculation [6-8, 22]. In our case, this was an observational pilot study and therefore a control group was not considered. However, we acknowledge the advantage of having a control group for future studies. In fact, the only randomized controlled trial involving microcirculatory dysfunction, which compared nitroglycerin versus placebo in septic shock patients, found that MFI improved over time in both groups in the setting of a strict background common resuscitation protocol [9]. Third, our study protocol considered microcirculatory reassessment only after completing the standard 12-hour HVHF procedure, and thus, we could have missed earlier effects. We selected a 12-hour design for two reasons: a) the first couple of hours after starting HVHF are characteristically unstable and patients are subjected to frequent fluid challenges or vasopressor titration that preclude a clear interpretation of microcirculatory changes; and b) because we were interested in evaluating the full effect of a 12-hour pulse HVHF session. Finally, it is still unclear if the sublingual microcirculation is representative of other organs [23, 24], so additional studies are necessary to assess the impact of HVHF over other microvascular beds.

**Conclusions**

The use of HVHF as a rescue therapy in patients with severe hyperdynamic septic shock is not associated to deterioration of sublingual microcirculation despite the increase in systemic vascular resistance. For the clinician this suggests that the increase in arterial pressure and SVRI, which is usually observed during HVHF is not at the expense of microcirculation. Furthermore, patients with the lowest values of sublingual microcirculatory blood flow
seem to improve this condition during HVHF. However, randomized controlled studies with HVHF in septic shock are required to confirm and better define the physiologic effects of HVHF on hemodynamics and perfusion.

References


