Pilot study on the effect of high dose dexamethasone on the sublingual microcirculatory flow in emergency admissions to intensive care

Y Hazewinkel, HM Oudemans-van Straaten, R van Raalte, DF Zandstra, PHJ van der Voort

Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Abstract - Objective To study the short-term effects on sublingual microcirculatory flow of high dose dexamethasone in critically ill patients. Setting/Patients In an observational prospective cohort pilot study patients were treated with dexamethasone (1 mg/kg). Patients treated with any steroid within seven days before inclusion were excluded. A sublingual sidestream dark field (sDF) measurement was taken before dexamethasone treatment and after 15, 30 and 60 minutes. The microvascular flow index (MFI) was determined (0 = no flow, 1 = intermittent flow, 2 = sluggish flow and 3 = normal flow). Measurements/Results The patients (n=21) had a median APACHE II score of 23. The median MFI improved from 2.58 (Inter Quartile Range, IQR, 0.65) to 2.92 (IQR 0.33) in the small vessels (p=0.004) and MFI also increased from 2.58 to 2.92 (p=0.06) in the medium sized vessels. The large vessels showed optimal flow anytime. The MFI improvement was, in a multivariate linear regression analysis unrelated to the use of vasoactive drugs or fluid balance. Conclusions The microcirculatory flow measured by sublingual sDF improves in the small vessels within the first hour of treatment in the ICU. The use of vasoactive medications and fluids was unrelated to this improvement. The administration of high dose dexamethasone was not associated with vasoconstrictive effects.

Keywords - microcirculation, dexamethasone, inflammation, critically ill, intensive care

Introduction
The acutely-admitted critically ill patient presents with a systemic inflammatory response syndrome characterized by an overproduction of inflammatory mediators and cytokines [1]. This inflammation has vasoactive effects [2]. Vasoconstriction leads to heterogeneity of blood flow and impairs tissue perfusion. Splanchnic vasoconstriction may lead to impaired intestinal barrier function due to ischaemia [3]. As a result, the gut will become permeable to microbial compounds such as endotoxins which may further impair the microcirculation by vasoconstriction [4]. Decreased microcirculatory blood flow will reinforce this process and as a result more vasoconstriction, tissue ischaemia and finally organ failure will occur [5]. During sepsis an associated phenomenon is the effect of mediators on the nitric oxide (NO) system. The NO regulation is altered during sepsis by the heterogeneous expression of inducible nitric oxide synthase (iNOS) [6-9]. Since iNOS is not expressed homogenously between and within organ systems, heterogeneity of flow occurs [7]. In contrast, areas with a high expression of iNOS have a high degree of NO-induced vasodilatation which may lead to either a good microcirculatory flow or shunting [6].

High dose dexamethasone can be given to intervene in the process of inflammatory mediator production, iNOS expression and induced vasoconstriction [9,10,11]. It was previously argued that glucocorticosteroids have vasoconstrictive effects [12]. However, since dexamethasone decreases the inflammatory response, the production of cytokines, the leucocyte adhesion to the vascular wall and iNOS expression [9,10,13] the effects on microcirculatory dysfunction may instead be beneficial.

For a few years it has been possible to monitor the microcirculation directly using the orthogonal spectral polarization (OPS) imaging technique [14]. Recently, a refined method called side stream dark field (sDF) imaging has been developed which has improved technology and image quality [16=15]. SDF and OPS provide new insights into the physiology of the microcirculation.

Based upon above mentioned theoretical considerations, we conducted a clinical observational pilot study on the short-term effects of high dose dexamethasone on the microcirculation as measured by sDF.

Materials and Methods
Study design and setting
The study was an observational prospective cohort pilot study in critically ill patients and was carried out in the ICU of a teaching hospital run by full-time intensivists. The unit is a twenty-bedded mixed medical, surgical and cardiac surgery intensive care.

The study was approved by the local ethics and scientific committee according to Dutch and European legislation. Since the study was observational, non-invasive and did not imply extra blood samples or treatment other than routine, the need for informed consent was waived by the committee.

Patients
Patients were enrolled consecutively for the study if they were emergency admissions for multiple organ failure and admitted during office hours. These patients were all designated to receive their first dose of dexamethasone intravenously by bolus injection.
Dexamethasone is routinely administered to achieve early shock reversal. Patients treated with dexamethasone or any other steroid within seven days before inclusion were excluded. After baseline measurement of haemodynamic parameters and microcirculatory blood flow using SDF, the patients were treated with dexamethasone 1 mg/kg as a bolus intravenous injection over 5 minutes. The study did not interfere with clinical decisions concerning vaso-active medication or any other treatment.

Visualizing the microcirculation

To visualize the sublingual microcirculation we used the SDF imaging technique. SDF imaging consists of a light guide surrounded by green light-emitting diodes whose light penetrates the tissue and illuminates the microcirculation. Haemoglobin absorbs the light which leads to real time imaging of blood flow shown on an LCD screen at the bedside [15].

The microcirculatory flow was observed with SDF before the patients received dexamethasone and measurements were repeated at 15, 30 or 45 and 60 minutes after the dexamethasone infusion. Steady images were obtained, avoiding pressure artefacts, from three different regions under the tongue after removal of saliva with gauze. The images were stored on digital videotape. Subsequently, the images were captured in 15-second video clips and saved on a computer in AVI format [16].

Measurements

The microvascular flow index (MFI) was used to analyze the sublingual microcirculatory flow. The vessels were separated into small (10-25 µm), medium (25-50 µm) and large vessels (50-100 µm) by using the diameter as cut-off value. Quantification of flow was scored as 0 (no flow), 1 (intermittent flow), 2 (sluggish flow) and 3 (normal flow). The observer was blinded for patient number and time of recording when rating the SDF images.

Each image was divided into four quadrants in which the flow was scored separately for each vessel. The score was the sum of each quadrant score, divided by the number of quadrants in which the vessel type is visible. The final MFI score was an average of the three different regions measured under the tongue [16].

Haemodynamic parameters and the dosage of drugs were obtained simultaneously with the measurement of the microcirculatory flow. All variables were collected before administering dexamethasone and 15, 30 or 45 and 60 minutes after administering the drug. Severity of illness was determined by APACHE II and APACHE IV score and the sequential organ failure assessment (SOFA) according to the definitions of the Dutch National Intensive Care Evaluation (NICE), which are based on the original definitions (www.stichting-NICE.nl). The kidney and hepatic components of the SOFA score were used as a measure of kidney and hepatic failure, respectively.

Fluid balance was calculated over a 60-minute period by adding up the amount of all fluids infused and subtracting fluid loss (urine, drains, etc.).

Outcome measures

The primary outcome measure was the change in MFI from baseline (before dexamethasone) to one hour after dexamethasone infusion. In addition, the relations between MFI, vasoactive medication and SOFA score were analyzed.

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 14.0.1 (SPSS Inc, Chicago, IL). Values are given as median and interquartile range (IQR). The nonparametric Wilcoxon signed ranks test was used to compare the MFI before the administering of dexamethasone with the MFI sixty minutes after the administering of dexamethasone. Regression analyses were used to evaluate the effect of fluid balance on microcirculatory flow. Multivariate linear regression analysis was performed with the change in MFI over a 60-minute period as the dependent variable and forwardly entered vaso-active medication dosage used in this 60-minute period. A two-sided P value <0.05 was considered to indicate statistical significance for all analyses.

Results

Twenty-one consecutive patients were enrolled. Baseline characteristics are presented in Table 1. The dosage of drugs and haemodynamic parameters are presented in Table 2. Central venous pressure (CVP) decreased from 19 mmHg to 14 mmHg during the 60-minute study period, despite a positive fluid balance of almost 250 ml. The numbers of patients treated with vasoactive drugs are presented in Table 2.

The microcirculatory flow and dexamethasone

Median and IQR of MFI values of small and medium size vessels are presented in Table 3. The MFI for the large vessels is not presented.
because these vessels showed an optimum MFI of three at all time points. The MFI for the small vessels increased significantly over the one-hour study period ($p = 0.004$).

The impact of vaso-active drugs (nitroglycerine, dopamine, enoximone and norepinephrine) on the change in MFI over the 60-minute period was assessed by multivariate linear regression analysis (Table 4). The increase in MFI for the small vessels was in this analysis not related to the administration and dose of nitroglycerine, enoximone, dopamine and norepinephrine (Table 4). Subgroup analysis of the patients without nitroglycerine treatment ($n=5$) showed, just as in the whole group, a significant improvement in MFI for the small vessels, from 2.88 prior to dexamethasone to 3.00 after 60 minutes ($p = .042$). Figure 1 shows all individual patient data. Patients with and without NTG are identified.

**MFI and fluid balance**

Regression analyses showed a limited positive correlation between the fluid balance and the MFI of small vessels one hour after dexamethasone administration ($r^2 = 0.215$). However, there was no correlation between the fluid balance and the change in MFI for the small vessels from baseline ($r^2 = 0.008$).

**Discussion**

In this observational pilot study which was designed to explore the potential short-term vasoactive effects of high dose steroids on the microcirculatory flow in a population of patients needing emergency ICU admission, a significant improvement in sublingual microcirculatory blood flow (MFI of the small vessels) was seen in the setting of combined administration of high dose dexamethasone, fluids and vasoactive drugs. The anticipated vasoconstrictive effect, which according to the literature, might have been expected was not seen [12]. In contrast, the findings in our study are concordant with a recent study on the vasoactive effects of hydrocortisone [17]. The main question is whether the improvement in microcirculatory blood flow that we observed was obtained by the administration of fluids and vaso-active drugs such as nitroglycerine, enoximone, dopamine and norepinephrine. Previous studies have shown that nitroglycerine induces improvement in microcirculatory blood flow in critically ill patients [18], and in patients with severe heart failure [19]. In our study we found that the patients without nitroglycerine also showed an increase in small vessel MFI (Figure 1). Apparently, in some patients microcirculatory flow can improve without the use of nitroglycerine. The short term effect on MFI of the other vasoactive drugs, individually or combined has not been studied before. In the study of Spronk et al, the MFI was suboptimal after the administration of fluids and dopamine and only increased after administration of nitroglycerine. This suggests that fluid and dopamine are not sufficient to improve microcirculatory flow. A recent study showed that after extensive macrocirculatory resuscitation which included enoximone, nitroglycerine did not show additional improvement in microcirculatory flow [20]. It should be emphasized that neither our study nor the study of Spronk et al analyzed the functional capillary density (FCD). The FCD, which measures the number of perfused capillaries, can theoretically be reduced in our patients whilst MFI increases. In addition, due to heterogeneity of microvascular flow in critically ill patients, the sublingual site that we studied does not necessarily reflect all capillary beds.

**Table 2.** Vaso-active drugs dosage in microgram per kilogram bodyweight per minute and macro-haemodynamic parameters over a 60-minute period. All data are expressed as median and (IQR) or absolute number with percentage (%). *Significant increase over a 60-minute period ($p=0.04$)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>PRIOR TO DEXAMETHASONE</th>
<th>15 MIN</th>
<th>30/45 MIN</th>
<th>60 MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dose</td>
<td>Number of patients (%)</td>
<td>dose</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2.5 (5.5)</td>
<td>14 (67)</td>
<td>3.3 (6.7)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>0.1 (0.4)</td>
<td>11 (52)</td>
<td>0.2 (0.4)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0 (0.0)</td>
<td>4 (19)</td>
<td>0.0 (0.01)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0 (2.25)</td>
<td>9 (43)</td>
<td>0.0 (2.3)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0 (5.35)</td>
<td>6 (29)</td>
<td>0.0 (5.4)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemodynamics</th>
<th>PRIOR TO DEXAMETHASONE</th>
<th>15 MIN</th>
<th>30/45 MIN</th>
<th>60 MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (/min)</td>
<td>99 (48)</td>
<td>100 (37)</td>
<td>95 (34)</td>
<td>96 (32)</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>19 (9)</td>
<td>15 (8)</td>
<td>15 (7)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>63 (21)</td>
<td>72 (36)</td>
<td>79 (35)</td>
<td>73 (18)</td>
</tr>
<tr>
<td>Central temp. °C</td>
<td>35 (2.0)</td>
<td>34.5 (2.7)</td>
<td>34.6 (3.5)</td>
<td>34.9 (3.6)</td>
</tr>
<tr>
<td>Peripheral temp. °C</td>
<td>27.4 (2.4)</td>
<td>27.5 (5.0)</td>
<td>28.2 (3.7)</td>
<td>28.7 (4.9)</td>
</tr>
<tr>
<td>Central minus peripheral temp. °C</td>
<td>7.5 (4.4)</td>
<td>7.7 (2.3)</td>
<td>7.5 (3.3)</td>
<td>6.4 (2.6)</td>
</tr>
</tbody>
</table>

CVP: Central Venous Pressure, MAP: Mean Arterial Pressure, Temp: temperature.
To distinguish the potential vasodilatory effect of dexamethasone from the other vasoactive interventions in our study, we performed an analysis of subgroups and a multivariate analysis to search for arguments regarding the presence or absence of vasoactive effects of high dose dexamethasone. Although there was a weak relation between change in MFI and fluid balance and dopamine dose was higher at the end of the 60-minute study period, the increase in small-vessel MFI appeared independent of vaso-active medication. In addition, the subgroup of patients without nitroglycerine also showed an increase in MFI. Because the study group was small, uncontrolled and non-randomized, these findings should be interpreted with caution.

Whatever the reason for the observed increase in MFI in the present study might be, the administration of dexamethasone in this setting was not associated with a decrease in microvascular flow, and the SDF images did not show more pronounced vasoconstriction after the administration of dexamethasone. In support of our findings, others have shown that high dose glucocorticosteroids have vasodilatory properties in vitro [21]. This was achieved by its direct action on the glucocorticoid receptor, which stimulated phosphatidylinositol 3-kinase and protein kinase Akt. The subsequent eNOs production led to vasodilation. This rapid effect was seen within 30 to 90 minutes because it did not need gene transcription [21]. The timing of administration and the presence of an inflammatory state may be an important denominator of the vasoactive effects of dexamethasone.

A decrease in central venous pressure (CVP) from 19 mmHg to 14 mmHg during the study period was observed, despite a positive fluid balance of almost 250 ml. This decrease in venous pressure is most probably caused by venous dilatation or improved cardiac output. A limitation of the study is that we have no insight in additional haemodynamic parameters such as cardiac output, SvO₂ and lactate. On the other hand, the association between these parameters and microcirculation is weak.

The administration of high dose corticosteroids to critically ill patients is not a standard procedure throughout the world, probably because most reviews and a meta-analysis have shown no reduction in mortality [22,23]. Nevertheless, some physicians continue to administer a single high dose of dexamethasone to acutely admitted patients to decrease the overproduction of proinflammatory cytokines with a more rapid shock reversal and aiming at more preserved organ function [23]. This line of thought, which is not in accordance with a number of guidelines, is based on the argumentation that previous high dose steroid studies were done on intensive care units with different baseline treatment than that of the intensive care units of hospitals that administer high dose corticosteroids. This baseline treatment concerns infection prevention with the use of selective digestive tract decontamination, low dose corticosteroid supplementation for adrenal failure for 5-7 days after admission and strict glucose control. A single high dose of dexamethasone may even preserve adrenal function in the critically ill by mitigation of the inflammatory response [24]. The presence of an overwhelming inflammatory response is the main reason to administer dexamethasone to critically ill patients. This intervention has a sound biological rationale. Amongst other

### Table 3. MFI for the small and medium-sized vessels. All data are expressed as median and (IQR)

<table>
<thead>
<tr>
<th></th>
<th>PRIOR TO DEXAMETHASONE</th>
<th>15 MIN</th>
<th>30/45 MIN</th>
<th>60 MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>2.58 (0.65)</td>
<td>2.67 (0.50)</td>
<td>2.58 (0.73)</td>
<td>2.92 (0.33)*</td>
</tr>
<tr>
<td>Medium</td>
<td>2.58 (0.49)</td>
<td>2.83 (0.43)</td>
<td>2.58 (0.56)</td>
<td>2.92 (0.22)**</td>
</tr>
</tbody>
</table>

*Small vessels before dexamethasone compared with the small vessels at 60 minutes demonstrates a significant increase (p=0.004, Wilcoxon signed ranks test).

**Medium vessels before dexamethasone compared with the small vessels at 60 minutes demonstrates a trend to increase (p=0.06, Wilcoxon signed ranks test).

### Table 4. Multivariate forwardly entered linear regression analysis of the vaso-active drugs on the change in MFI for the small vessels over a 60-minute period.

<table>
<thead>
<tr>
<th></th>
<th>BETA</th>
<th>T</th>
<th>P-VALUE</th>
<th>95%CI FOR BETA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.83</td>
<td>0.086</td>
<td>0.054 – 0.73</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>-0.19</td>
<td>-0.43</td>
<td>0.67</td>
<td>-1.2 – 0.77</td>
</tr>
<tr>
<td>Dopamine</td>
<td>-0.008</td>
<td>-0.35</td>
<td>0.73</td>
<td>-0.058 – 0.041</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>-0.022</td>
<td>-0.017</td>
<td>0.99</td>
<td>-2.8 – 2.7</td>
</tr>
<tr>
<td>Enoximone</td>
<td>-0.008</td>
<td>-0.11</td>
<td>0.92</td>
<td>-0.16 – 0.15</td>
</tr>
</tbody>
</table>
effects, corticosteroids inhibit nitric oxide production and prevent the rolling and adhesion of leukocytes (leucocyte-endothelial interaction). The observed increase in MFI within 60 minutes is relatively fast for effects via iNOS and cytokine inhibition as these effects have previously been shown to take 2-4 hours to occur [25]. On the other hand, effects on leucocyte rolling and adhesion can be seen within 30 minutes [13,26]. In addition, the vasodilatory effect by eNOS stimulation may also be apparent within 30 minutes [21]. If the observed vasodilatory effects in our study are related to dexamethasone infusion then it is most probably an effect mediated by combined inhibition of leucocyte-endothelial interaction and enhanced eNOS production.

Up to now only few clinical studies on the interaction between high dose corticosteroids and the microcirculation have been performed. The problem is that the clinical setting of an emergency admission to the ICU is complex and easily leads to confounding. This confounding is the main drawback of the present study and prevents us from making definite conclusions. However, a single infusion of high dose dexamethasone was, in this study, associated with improved microcirculatory flow of the small vessels and not with signs of vasoconstriction. This preliminary study justifies a randomized clinical study on the vasoactive effects of high dose steroids in critically ill patients with an acute systemic inflammatory response.

In conclusion, we have shown by measurement with SDF that within the first hour of treatment in the ICU the microcirculatory flow improves. The use of several vaso-active medications and fluids was unrelated to this improvement. The concomitant administration of high dose dexamethasone was not associated with vasoconstrictive effects.

References