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Changes in the volume status of haemodialysis patients are reflected in sublingual microvascular perfusion

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Abstract

Background. After the introduction of sidestream darkfield imaging (SDF) of the microcirculation, it has become clear that in sepsis, microcirculatory alterations can exist in the absence of systemic haemodynamic abnormalities. However, it is unclear whether this phenomenon also occurs in the treatment of end-stage kidney disease (ESKD) where alterations in the volume status of patients occur during dialysis. We tested the hypothesis that volume changes during dialysis directly affect the perfusion of the microcirculation in a group of adult haemodialysis patients. Secondly, we evaluated microcirculatory response to autotransfusion using the Trendelenburg position (TP).

Methods. Patients who were on chronic intermittent haemodialysis were assessed for sublingual microvascular flow by SDF imaging pre- and post-TP, performed before and after ultrafiltration (UF). Sublingual microvascular flow was estimated using a semi-quantitative microvascular flow index (MFI) in small (diameter <25 μm, which includes capillaries), medium (25–50 μm) and large-sized (50–100 μm) microvessels (no flow: 0, intermittent flow: 1, sluggish flow: 2 and continuous flow: 3). Changes were evaluated with the non-parametric paired Wilcoxon test. $P < 0.05$ was judged to indicate a significant difference.

Results. Thirty-nine adult patients took part in the study. The underlying diseases causing ESKD were predominantly hypertension (HT, $n = 10$), diabetes mellitus (DM, $n = 7$) or both ($n = 3$). At the start of UF, microvascular flow did not change significantly by TP. After completion of UF, MFI had decreased significantly in all types of microvessels ($P < 0.001$). After UF (median volume extraction 2.49l), MFI was lower than that at the start of UF and increased in most patients after TP ($P < 0.001$) in all categories of vessels. Changes were most prominent in the smallest microvessels.

Conclusions. Sublingual microvascular perfusion is reduced by UF and can be restored temporarily using autotransfusion by TP due to increased venous return. SDF imaging is able to detect these volume changes. SDF imaging and TP could become a useful bedside tool to evaluate the patient's (microvascular) volume status and response to therapy in dialysis or intradialytic hypotension.

Keywords: haemodialysis; microcirculation; sidestream darkfield imaging; Trendelenburg position; ultrafiltration

Introduction

The introduction of orthogonal polarization spectral (OPS) imaging and its technical successor sidestream darkfield (SDF) imaging has opened challenging new perspectives in *in vivo* research of microcirculatory alterations. In Figure 1, an image and a short explanation of this technique is shown. As has been shown previously by Boerma *et al*., this technique can be used to express the rate of microvascular flow semi-quantitatively, a method with a proven good inter- and intraobserver resemblance [1]. Most of the studies using this technique have been conducted under states of (septic) shock [2–4]. During haemodialysis, only indirect measurements of the microcirculatory perfusion in humans have been described, in small subgroups.

During haemodialysis for renal replacement therapy in chronic renal failure, patients are exposed to intermittent changes in intravascular volume states due to controlled ultrafiltration (UF) of several litres in a few hours. This phenomenon is associated with haemodynamic instability in 25–55% of the dialysis sessions, called intradialytic hypotension, and lower extremity muscle cramping [5,6]. It is a significant problem, as hypotension persisting until after dialysis is associated with an increased risk of death and a reduction of the possibility of regaining renal function in patients with acute renal failure (like renal tubular acidosis) [7]. Besides a number of physiologic changes occurring during dialysis that may decrease (micro-) vascular perfusion, such as increased blood viscosity, increased platelet aggregation, decreased erythrocyte deformability and increased

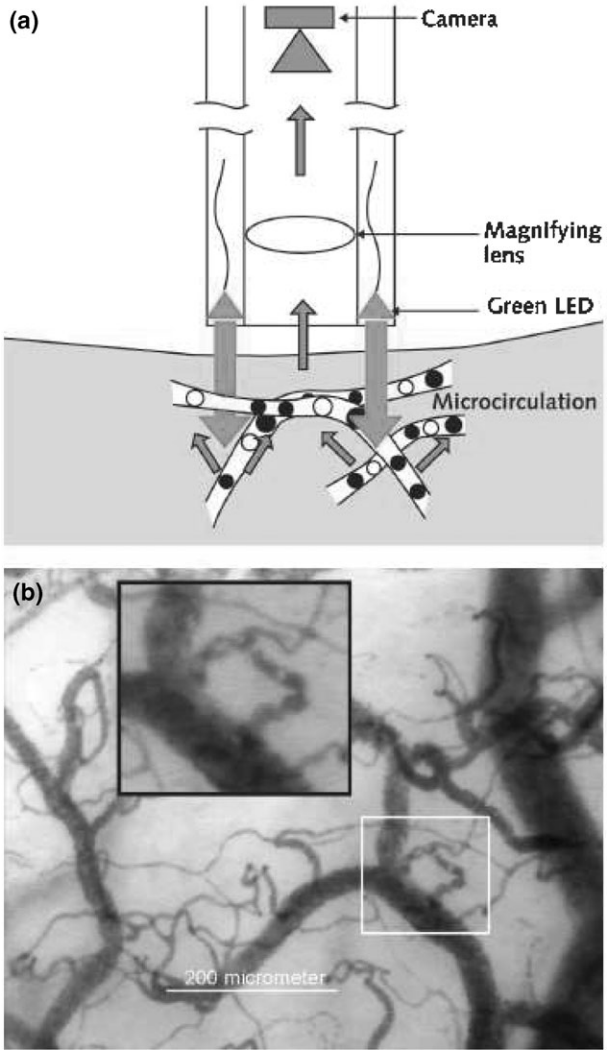


Fig. 1. SDF imaging. From [2].

haematocrit, a reduction in blood volume is crucial in its pathogenesis [6]. Pre- and post-dialysis, the occurrence of low intravascular volume hypotension is routinely monitored by measuring orthostatic blood pressure and heart rate, as well as frequently measuring haematocrit. Treatment of intradialytic hypotension includes the stopping of, or decreasing, the rate of UF and replacing the intravascular volume with either saline, albumin or hydroxyethylstarch (HES) infusions [8]. This is done with small volumes, to not totally offset the amount of ultrafiltrated volume. However, the first approach is often to place the patient in Trendelenburg position (TP), a standardized pelvis up, head-down position as described elsewhere [9–11].

TP may be used as an elegant and effective alternative to giving a fluid challenge to unmask hypovolaemia and identify patients who may respond to volume infusion [11–13]. Venous blood from the legs is propelled to the intrathoracic compartment, thus increasing cardiac preload and enhancing cardiac output [11–13]. As this manoeuvre is completely reversible and its effects are only temporary, patients who do not respond well to the increase in intrathoracic volume can be withheld from the detrimental effects of intravenous volume infusion. Data about the effect of TP on haemodynamic parameters during dialysis or intradialytic hypotension are lacking.

In the present clinical study, we tested the hypothesis that a controlled change in intravascular volume status during UF is reflected by sublingual microcirculatory hypoperfusion and can be detected by SDF imaging. Secondly, we assumed that these microcirculatory changes could be reversed by autotransfusion using TP.

Subjects and methods

The study was approved by the medical ethics committee. According to the guidelines of our hospital, informed consent is not required when standard therapy is monitored by non-invasive techniques. Underlying diagnosis, current medication and haemodynamic data were collected for later analysis. Adult patients were asked to participate in the study if they were $\geq$18 years of age and treated with chronic intermittent haemodialysis in the nephrology unit of the Gelre Hospitals, between September 2005 and April 2007.

Measurements

Patients were included during regular haemodialysis sessions. All patients were on a dialysis schedule of three times weekly using a Fresenius F8-HPS low-flux dialyser or Fresenius FX60 high-flux dialyser as part of the extracorporeal circuit on the Hospal Integra dialysis monitor. The composition of the dialysis fluid was constant during treatment. UF was at a constant rate and calculated to reach a previously assessed dry weight or target end-dialytic weight during treatment hours. The dry weight or target end-dialytic weight was previously determined by the treating dialysis doctor by adapting it to clinical parameters such as the absence of oedema and the occurrence of symptoms of manifest hypovolaemia after previous dialysis sessions in each patient. Just before starting UF, microvascular measurements were done. The measurements were done at baseline (T = 1), during TP, before the beginning of UF (T = 2), just after the end of UF (T = 3) and during TP just after the end of UF (T = 4). Haemodynamic variables were recorded before and after UF at the same time points. For TP, the patient was put in a standardized TP for 1 min before microvascular measurements were performed. The dialysis chair was tilted in such a way that the head is 20 cm below the feet. This position is standardized and a feature of the dialysis chairs.

Microvascular imaging and flow quantification

Patients were assessed for sublingual microvascular perfusion by sidestream darkfield (SDF) imaging [2] (Microscan^{TM}, Microvision Medical, Amsterdam, the Netherlands), before and 1 min during TP (see Figure 1a and b). For SDF imaging, a 5× objective was used during all measurements with an on-screen magnification of 286×. Streaming video images were captured through fire wire connection to a laptop computer. SDF imaging and semi-quantitative analysis were performed in a standardized way as described in detail elsewhere [1]. In short, SDF images were obtained from three different regions within the site of interest and each image was divided into four equal quadrants. Quantification of flow (no flow: 0, intermittent flow: 1, sluggish flow: 2 and continuous flow: 3) was scored per quadrant for each cohort of vessel diameter (small sized: <25 μm, which includes capillaries, medium sized: 26–50 μm and large sized: 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. To exclude observer bias, scoring of movies was done off-line in random order by a second investigator who was blinded from the clinical setting.

Statistics

SPSS/PC+ (version 13, SPSS Inc., IL, USA) was used for statistical analysis. Values were expressed as median and interquartile range (IQR). Given

the relatively small sample sizes, we decided to restrict to nonparametric tests. Wilcoxon's paired rank-sum test was used to detect changes in parameters. Correlations were tested with Spearman's test. A P-value <0.05 (two-sided) was considered significant.

Results

Patients

Thirty-nine patients (24 males, 15 females; median age 67.2 [IQR 58.8–75.3] years) on chronic haemodialysis were included in our study. The underlying diseases causing end-stage renal disease were predominantly hypertension ($N = 10$), diabetes mellitus ($N = 7$) or both ($N = 3$). The other patients had cystic kidneys (3), chronic infections (1), unknown cause of renal failure (6), amyloidosis (1), multiple myeloma (1), cholesterol embolisms (1), renovascular renal failure (1) and chronic glomerulonephritis. Patient characteristics according to different causes of renal failure are shown in Table 1. The use of anti-hypertensive medication was recorded; between 0 and 3 different types of anti-hypertensive drugs were used per patient, predominantly ACE inhibitors and beta-blockers (Table 1).

Haemodialysis and ultrafiltration

All patients were clinically stable, and no intravenous fluids were administered during haemodialysis. A median volume of 2.49 l [IQR 1.63–3.45, mean 2.48] was removed in median 4.0 h [3.5–4.0, mean 3.79]. Blood pressure decreased during UF; the median systolic value decreased non-significantly from 135 [120–149, mean 135] to 126 [109–145, mean 129] mmHg ($P = 0.055$) and the median diastolic blood pressure decreased significantly from 73 [65–80, mean 73] to 66 [55–85, mean 68.6] mmHg ($P = 0.049$). There was no significant change in heart rate, before (median 75 [70–85, mean 76] beats per minute) and after UF (79 [73–84, mean 78] beats per minute) ($P = 0.053$).

Microvascular measurements

Median baseline (T = 1) MFI value was 2.8 [IQR 2.5–3.0] in the small vessels, 2.8 [2.5–3.0] in medium-sized vessels and 3.0 [2.8–3.0] in large vessels. Values in healthy controls have been previously described; the MFI is 3.0 in all vessel types with a very small SD [14]. When TP was applied before UF (T = 2), there was no significant change in MFI in all types of vessels (small, medium-sized and large); the MFI values were 3.0 [2.8–3.0], 3.0 [2.8–3.0] and 3.0

Table 1. Patient characteristics

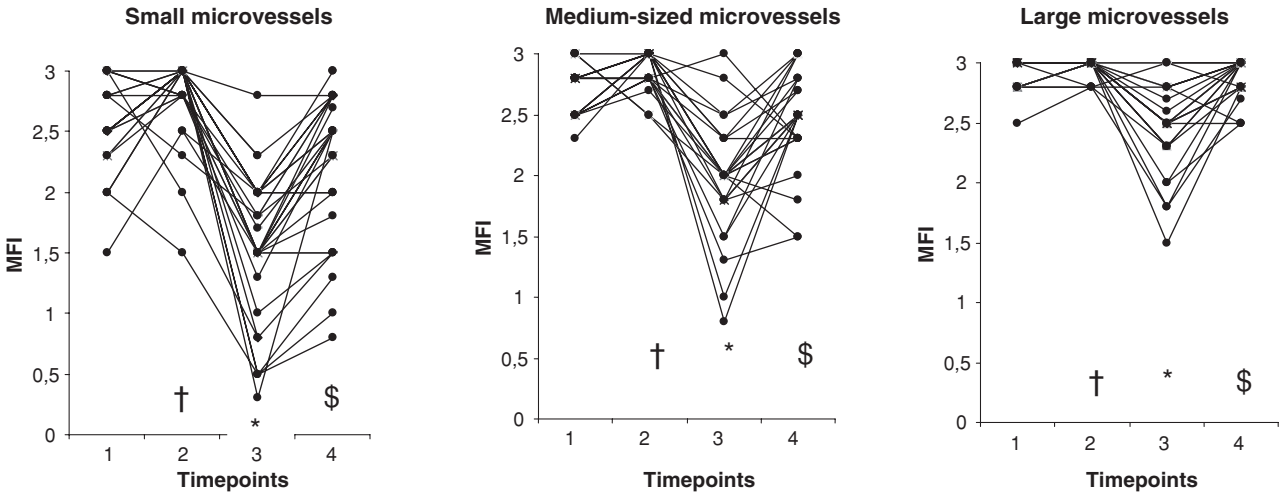
	All patients $N = 39$	Diabetes mellitus $N = 7$	Hypertension $N = 13$	Other causes of renal failure $N = 19$
Male/female	24/15	5/2	6/7	13/6
Age (years)	67 [59–75]	62 [53–67]	69 [63–82]	68 [59–75]
Years on haemodialysis	2 [1–5]	3 [2–5]	3 [1–4]	2 [1–5]
24-h urine volume (ml)	600 [0–900]	600 [215–950]	700 [0–840]	300 [0–890]
Ultrafiltration volume (l)	2.49 [1.63–3.45]	2.89 [2.54–3.65]	2.49 [1.98–3.19]	2.34 [1.19–3.58]
Use of beta-blocker	13 (33%)	1 (14%)	4 (31%)	8 (42%)
Use of ACE inhibitor	15 (38%)	3 (43%)	4 (31%)	8 (42%)
Use of other antihypertensives	13 (33%)	0 (0%)	5 (38%)	8 (42%)

Data are expressed as numbers or median [interquartile range].
No significant differences between the groups could be found.

Table 2. Percentage change in MFI due to ultrafiltration (decrease) or Trendelenburg position after ultrafiltration (increase) according to vessel size

Change in MFI (%)	Decrease by ultrafiltration (T1 → T3)			Increase by Trendelenburg (T3 → T4)		
	Small	Medium	Large	Small	Medium	Large
0–25	11	14	28	9	18	26
26–50	14	18	6	9	9	4
51–100	9	2	0	12	3	2
>101	0	0	0	2	2	0
No data	5	5	5	7	7	7
Total	39	39	39	39	39	39

MFI = microvascular flow index.
T = 1, before ultrafiltration (UF) and before TP.
T = 3, after UF and before TP.
T = 4, after UF and during TP.
No data: no scoring of flow possible.
Small = diameter <25 μm (includes capillaries).
Medium = diameter 25–50 μm.
Large = diameter 50–100 μm.



T = 1: before UF and before TP
T = 2: before UF during TP
T = 3: after UF and before TP
T = 4: after UF during TP

†: no significant change from T=1 to T=2 (p>0.05)
*: significant change from T=3 compared to baseline T=1 (p<0.001)
$: significant change from T=3 to T=4 (p<0.001)

MFI = microvascular flow index

Note: due to overlapping points and lines not all individual values are visible in the graph.

Fig. 2. Microvascular flow changes due to ultrafiltration and Trendelenburg's.

[3.0–3.0], respectively (Figure 2). In contrast, after UF had been performed (T = 3), the median MFI value was lower in small (1.5 [1.5–2.0]), medium (2.0 [1.8–2.0]) and large (2.5 [2.3–2.8]) microvessels when compared to baseline (all $P < 0.001$). When TP was performed after UF (T = 4), the MFI increased in small (2.5 [2.0–2.8]), medium (2.5 [2.3–2.7]) and large microvessels (3.0 [2.8–3.0]); all $P < 0.001$. In Table 2, the percentage of change in MFI can be seen as a result of UF (decrease) or TP after UF (increase) according to vessel size.

No significant correlation could be found between the change in MFI in any of the different vessels types on the one hand and the UF volume expressed as percentage of dry body weight on the other. In addition, this absence of any correlation was not affected by the application of TP, nor by the different clinical subgroups (DM, HT and other causes of renal failure).

Thirteen patients (33%) used a beta-blocker; the subgroup analysis revealed no correlation between the use of a beta-blocker and change in MFI. There were no significant changes in MFI values in any of the different microvessel sizes between patients using an ACE inhibitor or angiotensin receptor antagonist and patients not using one of these, at baseline as well as after the first Trendelenburg manoeuvre.

Discussion

In this study we have investigated, to our knowledge for the first time, the impact of UF on microcirculatory perfusion by direct observation using SDF in adult patients on chronic renal replacement therapy. Our findings show that there is a substantial reduction in sublingual microvascular flow in patients after UF. This affect was most pronounced in the smallest microvessels. Our study further showed that this microvascular hypoperfusion could be corrected effectively by autotransfusion induced by TP.

Several studies have investigated the response of haemodialyis on microcirculatory perfusion, using indirect observation methods, with results resembling our findings. Weiss *et al*. and Hinchcliff *et al*. showed decreases in transcutaneous oxygen pressure (tcPO2) during and shortly after haemodialysis [15,16]. Beckert *et al*. found a non-significant decrease in blood flow after dialysis in diabetic patients using venous oxygen saturation and relative blood flow using a spectrophotometer [17]. All these studies were hampered by very small groups, and transcutaneous PO2 may be decreased by a number of other factors than microvascular perfusion in the ESKD-chronic dialysis population. Furthermore, it is difficult to compare the results of those studies with our data, as we did not assess tcPO2.

While there was a marked reduction of microcirculatory perfusion after UF in our patient group, there was only a small decrease in both systolic and diastolic blood pressure with no increase in heart rate. This is not an unexpected finding, as decreasing local microcirculatory blood flow in compliant vascular beds is an important mechanism to maintain systemic haemodynamics [18]. On the other hand, patients with end-stage kidney disease frequently develop desensitization or loss of autonomic control, because of problems with endothelial dependent vasodilation (EDV) due to decreased availability of NO, having direct involvement in intradialytic hypotension and poor/lack of compensatory HR response. We should emphasize that patients on haemodialysis are generally not hypovolaemic after

dialysis, although hypotension can be pronounced. They are merely normovolemic, but intravascular volume has decreased rapidly due to dialysis, and as a result, interstitial fluid is shifting to the intravascular compartment. In the first period after dialysis, there can be intravascular hypovolaemia, but the total body fluid volume is normal.

In this study, we showed that an induced decrease in intravascular volume by UF causes a marked reduction in microcirculatory perfusion and that correction of microcirculatory hypoperfusion can be achieved by using TP. In this way, our study revealed the reaction of microcirculatory perfusion on volume changes, a largely unknown area. Two mechanisms may explain the effect of TP on microvascular perfusion. Firstly, there is a direct effect of TP on systemic haemodynamics. TP increases venous return by shifting venous blood from both legs to the intrathoracic compartment [19,20], and improves cardiac output by increasing the left and right ventricular preload [12,13,21,22]. It thus serves as an autotransfusion. However, this is only a temporary effect, as is shown by Gaffney *et al*. [23,24]. On the other hand, a component of venous congestion induced by gravitational force due to TP might play a role, as we measure microcirculation in the head compartment, the lowest point during TP. The combined effect of these two mechanisms is uncertain.

The observed effects may have been influenced by the left ventricular mass index (LVMI) of the patients. Although we did not measure LVMI, this value is known to be increased in ESKD patients with concomitant effects on autoregulatory capacity for maintaining arterial pressure during decreases in the cardiac preload [25].

Several limitations in our study should be mentioned. One potential concern using TP is the possible induction of sympathetic activation with influence on the microcirculation perfusion itself by placing patients with their head downwards. However, no significant differences in pulse rate could be demonstrated in our study during TP, which may be interpreted as a surrogate parameter of autonomic activation. This effect is therefore probably of minor importance in our study. On the other hand, 13 of the 39 patients used a β-blocker, which might have influenced this parameter.

Since there is no valid method to measure extracellular fluid volume, and ultrafiltrate/dry body weight ratio may not reflect this accurately, further research that combines direct observation of microcirculatory blood flow by means of SDF with muscle sympathetic nerve activity measurements during dialysis might contribute to further elucidation of this concept, with extensive potential clinical relevance.

Furthermore, as this was an observational study conducted in patients undergoing their regular haemodialysis sessions, it was not an option to show if the microvascular changes were reversible with volume infusion, which, from a scientific point of view, would have been interesting.

We have no data on weight gain since last dialysis and occurrence of symptoms on dialysis; we therefore cannot correlate changes in microcirculatory flow to symptoms. Due to our study population, we also did not measure cardiac output or central venous pressure, which would have given more information about the systemic haemodynamics. As our last measurement was shortly after stopping haemodialysis, we probably did not measure the effect of plasma-refill, which might restore the abnormalities in flow we described.

In addition, measurements of sublingual microvascular perfusion itself may be hampered by technical difficulties like a moving tongue, inability to obtain stable and evaluable images, respiratory artefacts and local pressure applied, especially in a non-sedated group of patients. Due to these technical difficulties, we miss data in 5 of the 39 patients (12.8%) and 7 of the 39 patients (17.9%) when judging the effect of UF or TP, respectively. However, the evaluation of inter- and intraobserver variability of this technique was recently studied by Boerma *et al*. [1] and confirmed by Trzeciak *et al*. [14]. They showed, with all potential inaccuracies kept in mind, that these images can be quantified in a reproducible way. Although technical limitations may play a role in obtaining the images and training in the use of a microvascular imaging device is required in general, these effects are probably equally present in all patients.

Due to a decrease in intravascular volume during HD or UF, vasoconstriction occurs in the microcirculation, which reduces haematocrit as is shown by Duling [26]. Therefore, rheological changes occurring during HD or UF, especially in the smallest vessels, are to be expected and influence microvascular perfusion again.

Finally, patients on haemodialysis cannot be compared to the general population with respect to microcirculatory behaviour, as most of these patients have underlying diseases that are known to have an effect on the microcirculation (diabetes, hypertension, etc.). Extrapolation of our findings should thus be done with care.

In conclusion, we showed that sublingual microvascular perfusion is decreased after a controlled decrease in intravascular volume using UF, particularly in the smallest microvessels (<25 μm), and that this hypoperfusion can be reversed by TP. These changes could be detected using SDF imaging. SDF imaging is non-invasive and can be used easily at bedside [27]. Therefore, using SDF imaging to monitor the microcirculation, in combination with TP, could become a valuable tool to non-invasively assess the volume status in patients. This might be of value in dialysis or episodes of intradialytic hypotension, but more studies are needed to determine its precise clinical value.

Conflict of interest statement. Besides his affiliation listed above, C.I. is chief scientific officer of a company called Translational Physiology. Translational Physiology is a university-based company dedicated to the development of optical spectroscopic tools for study of the microcirculation and tissue oxygenation such as the SDF imaging used in the current study. In this context, he holds patents and shares.

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