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Acute effects of haemodialysis on cutaneous microcirculation in patients with peripheral arterial occlusive disease

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Abstract

Background. Peripheral arterial occlusive disease (PAOD) is an increasing problem in patients on maintenance haemodialysis. Alterations in microvascular perfusion accompany and complicate arteriosclerosis of large vessels and might contribute to the disease process. The aim of the study was to investigate the acute effects of haemodialysis on the cutaneous microcirculation in 26 patients with and without intermittent claudication.

Methods. Cutaneous perfusion was assessed by measuring transcutaneous oxygen pressure ($tcPO_2$) and skin temperature at the dorsum of the foot. After standardized cooling to 15°C of a 2 cm^2 skin area, the time to reach baseline skin temperature was evaluated as an indirect parameter of reactive hyperaemia.

Results. During haemodialysis, $tcPO_2$ dropped significantly in both groups. The decrease in $tcPO_2$ was more pronounced in patients with PAOD (20% *vs* 15% n.s.). The reactive hyperaemia response was reduced significantly in patients with intermittent claudication indicated by a prolonged time to reach baseline skin temperature after cooling. Values of $tcPO_2$ and reactive hyperaemia did not reach baseline values at the end of haemodialysis in either group.

Conclusions. Nutritive skin perfusion is impaired during haemodialysis. These changes are more pronounced in patients with PAOD and persist after dialysis. These findings are relevant for the treatment of patients with vascular disease on maintenance haemodialysis.

Key words: arteriosclerosis; cutaneous microcirculation; haemodialysis; peripheral arterial occlusive disease; transcutaneous PO_2

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Introduction

The number of patients with end-stage renal disease, particularly secondary to diabetes mellitus, continues to grow by ~8–10% per year [1,2]. Arteriosclerosis and its complications are a highly prevalent clinical problem in long-term haemodialysis patients. Cardiovascular mortality is increased ~20-fold in dialysis patients compared with the general population [1]. There is increasing evidence that the arteriosclerotic process is accelerated in uraemic patients [3–6]. In the past, interest was focused primarily on coronary heart disease [7,8]. Less attention was paid to peripheral arterial occlusive disease (PAOD), which also greatly affects morbidity and quality of life of uraemic patients.

The mechanisms of the accelerated arteriosclerotic process in uraemic patients are not fully understood. An association between an altered calcium/phosphate metabolism and arteriosclerosis has been reported [3,9]. It has also been suggested that haemodialysis itself may contribute to arteriosclerosis [5]. However, the differentiation of the progress of arteriosclerosis before and during dialysis therapy is difficult. This explains why the observed acceleration of the arteriosclerotic process in uraemic patients is still poorly understood. Arteriosclerosis of large vessels is accompanied and complicated by alterations in microvascular perfusion (downstream dysregulation [10]). The disturbed microcirculation itself could contribute to the progression of the arteriosclerotic process, e.g. by leukocyte activation or hypoxia-induced proliferation of smooth muscle cells [11]. Some patients suffer hypoxic episodes such as angina pectoris or rest pain in their feet during dialysis. This might be the result of an altered perfusion of the microvessels in the absence of macrohaemodynamic changes. In addition, quantitative and qualitative structural changes in the cutaneous microvasculature, e.g. reduced capillary density or increased tortuosity, were described in patients on maintenance haemodialysis [12–15]. To test the hypothesis of microcirculatory dysregulation in dialysis patients, the acute effects of haemodialysis on the

cutaneous microcirculation were measured in chronic haemodialysis patients with or without PAOD.

Subjects and methods

Patients

Twenty-six patients on chronic maintenance haemodialysis (15 females and 11 males) with a median age of 65.5 years (range 38–81 years) were included. The mean duration of dialysis was 8.1 years. The underlying renal diseases are given in Table 1. The patients were dialysed 3×4–5.5 h per week using AK 10 (Gambro Co., München, Germany) or MTS 2008 C (Fresenius Co. Bad Homburg, Germany) dialysis equipment. Thirteen patients had PAOD with a pain-free walking distance of between 50 and 200 m on treadmill testing (12% slope, velocity 3 km/h) according to Fontaine stage II. The vascular lesions were confirmed by duplex scanning and/or angiography. Seven patients had occlusions of the superficial femoral artery, three patients had co-existing above and below knee occlusions and three had occlusions distal to the popliteal artery. In the control group, significant vascular disease was excluded by the following tests: ankle/arm index at rest and after exercise >0.9; unlimited walking distance; no trophic skin changes; and absence of mediacalcinosis. The risk factor profile of both groups is summarized in Table 2.

Methods

As a parameter of the quality of nutritive skin perfusion, transcutaneous oxygen pressure ($tcPO_2$) was determined. $tcPO_2$ was measured continuously using a three-channel recorder (Oxymonitor 236 065 02, Hellige GmbH, Freiburg, Germany) with an electrode temperature of 44°C at a constant room temperature of 21°C [16–18]. In patients with PAOD, the leg with the lower peripheral perfusion was used for placing two probes at the forefoot and dorsum of the foot. The third probe was attached to the forefoot of the contralateral lower leg which served as control. In patients without PAOD, the electrodes were located on either foot. The electrodes were placed 15 min prior to puncturing the vascular access allowing a stabilization of the $tcPO_2$ values. Insertion of the arterial and venous lines did not influence the $tcPO_2$. The patients were haemodialysed in a semi-reclined position. During the dialysis procedure, the $tcPO_2$ was recorded every 30 min up to 240 min (T0–T8). The mean value from the two probes on one foot was calculated and used for statistical analysis. Between the two measurement sites, a temperature sensor was fixed. Skin temperature was recorded at the beginning of haemodialysis, after 120 min and after 240 min. A skin area of 2 cm^2 around the temperature wire was cooled to 15°C with a metal stamp, and time to reach baseline skin temperature was measured (0, 120 and 240 min). This time served as an indirect parameter of reactive hyperaemia and of maximum total skin blood flow. Systemic blood pressure was monitored throughout the dialysis procedure; blood pressure readings at 0, 120 and 240 min were used for analysis. The data are presented as mean $\pm$ standard error of the mean. The paired and unpaired *t* tests were used for statistical analysis. The level of significance was 5%.

Table 1. Primary renal disease of haemodialysis patients

Renal disease	Patients (*n*)
Diabetes mellitus	5
Analgesic nephropathy	4
Glomerulonephritis	3
Hypertension	3
Ischaemic nephropathy	2
Gouty nephropathy	2
Polycystic renal disease	2
Unknown	5

Results

The resting $tcPO_2$ values in both groups were in the normal range and did not differ significantly (control: 59 ± 2 mmHg, PAOD 62 ± 3 mmHg, n.s.). During haemodialysis, $tcPO_2$ decreased significantly in patients with and without PAOD. Transcutaneous oxygen pressure values for each patient are summarized in Table 3. The largest decrease in $tcPO_2$ was from 59 ± 2 mmHg to 50 ± 3 mmHg in patients without vascular disease ($P < 0.0005$) and from 62 ± 3 mmHg to 50 ± 4 mmHg in patients with PAOD ($P < 0.0002$). Although the decrease in patients with PAOD tended to be more pronounced, no statistical difference was found between the two groups. Mean $tcPO_2$ at the indicated time points is presented in Figure 1. The decrease in $tcPO_2$ reached its maximum between 90 and 120 min. $TcPO_2$ increased slightly to the end of dialysis without reaching baseline values. No patient reported angina pectoris or leg discomfort.

Blood pressure response during the dialysis session varied between the patients: 10 patients showed a slight decrease of <10 mmHg, 11 patients showed a reduction of up to 20 mmHg, and five patients experienced a fall of >20 mmHg. Although more patients with a pronounced drop in $tcPO_2$ had a fall in blood pressure of >20 mmHg, a significant correlation could not be established (Table 4). Skin temperature increased in

Table 2. Risk factor profile of patients

	No.	Gender		Age	Diabetes	Hypertension	Smoking	Hyperlipidaemia	Obesity
		m	f						
All	26	11	15	65.5	7	14	5	12	9
Control	13	5	8	68.8	1	5	2	5	3
PAOD	13	6	7	62.2	6	9	3	7	6

Table 3. $tcPO_2$ values of each patient during haemodialysis (mmHg)

Patient	T0	T1	T2	T3	T4	T5	T6	T7	T8
Controls									
1	65.5	64.5	61.5	57	51	48	44.5	45	44
2	75	73	75	70.5	76	75.5	75.5	77	75
3	51	56	56.5	50.5	42.5	46	46	48	51
4	51	51	49	51.5	42	46	51	58	54.5
5	63	60.5	46	40	40.5	44.5	41	42	48
6	53	52	43.5	45	43.5	49.5	48	51	49
7	65.5	69	67	66.5	70	68.5	71.5	70	71
8	54	51.5	51.5	54	58	58	56.5	58.5	60
9	48.5	53.5	45.5	43.5	46	48.5	47	55	54
10	68	66	64.5	65.5	67.5	63.5	67	69	71.5
11	58.5	60.5	47	50.5	51.5	56	48.5	49.5	52.5
12	50.5	50	44.5	44	47	51.5	50	46	45
13	65.5	68	63	57	57.5	59	50	53	57
mean	59.1	59.6	55	53.5	53.5	55	53.6	55.5	56.3
SEM	2.3	2.2	2.9	2.6	3.2	2.7	3.0	3.0	2.9
PAOD									
A	40.5	40	40	41.5	39	39	43.5	44.5	44
B	51.5	52.5	48	36.5	39	36.5	37.5	41	42
C	61.5	62	58.5	54.5	53.5	54.5	52.5	55.5	58
D	62	60.5	57	58.5	57.5	60	58	57.5	58.5
E	60	59.5	50	39.5	40	34.5	33	32	32
F	72.5	75.5	74.5	69	68	75	76.5	75.5	76.5
G	55	58	44	45	49	50.5	52	40.5	43.5
H	75.5	82.5	77.5	75	77.5	76	79	77	78
I	57.5	52.5	49	44.5	40.5	41	42	49.5	46
J	64	61	61.5	60	67	66.5	67.5	70	73.5
K	70.5	7.4	70	72.5	68	67.5	73.5	76	79
L	84	79.5	65.5	56	56.5	54.5	48	48	49
M	50	42.5	33.5	36.5	35.5	48	41	44	44
mean	61.9	61.5	56.1	53	53.1	54.1	54.1	54.7	55.7
SEM	3.2	3.7	3.7	3.8	3.9	3.9	4.3	4.2	4.5

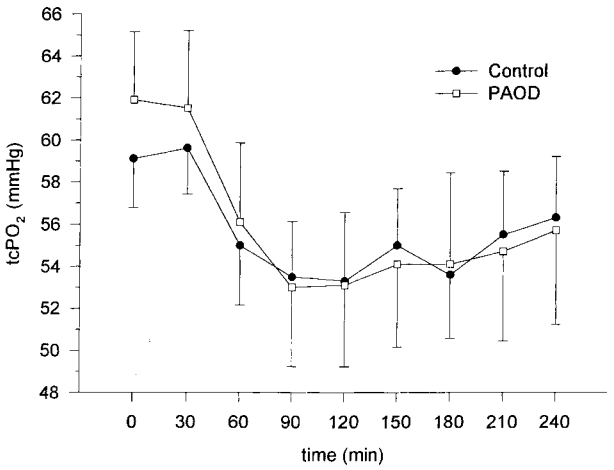

Fig. 1. Mean $tcPO_2 \pm$SEM (mmHg) during haemodialysis in controls and patients with PAOD.

Table 4. Correlation of decrease in $tcPO_2$ and blood pressure (POAD: control)

$tcPO_2$ drop RR fall	<5 mmHg	<10 mmHg	>10 mmHg
<10 mmHg	4 (2:2)	4 (4:0)	2 (2:0)
<20 mmHg	6 (2:4)	1 (0:1)	4 (1:3)
>20 mmHg	0	1 (0:1)	4 (2:2)

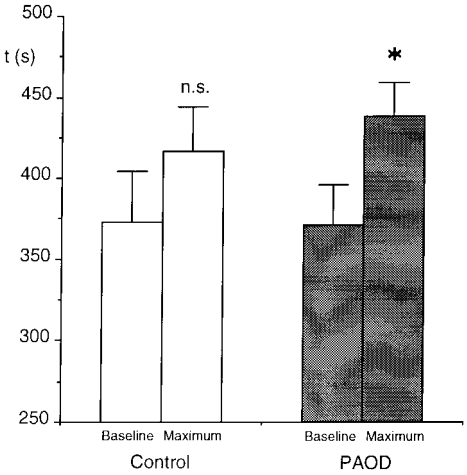

Fig. 2. Time to reach baseline skin temperature $\pm$SEM (s) after local cooling during haemodialysis in controls and patients with PAOD.

both groups significantly to a similar extent (control: $31.6°C \pm 0.4°C$ to $33.7°C \pm 0.2°C$, $P<0.05$; PAOD $31.1°C \pm 0.5°C$ to $33 \pm 0.2°C$, $P<0.05$). No relationship was found between $tcPO_2$ and skin temperature.

The time to reach baseline skin temperature (tbt) after standardized cooling increased during haemodialysis in patients with PAOD significantly from 371 ± 25 s to 438 ± 21 s. The increase of tbt in controls from 373 ± 31 s to 417 ± 27 s did not reach statistical significance (Figure 2). Patients with a large decrease in $tcPO_2$ tended to have a pronounced extension of tbt.

No correlation was found between the investigated parameters and age, fall in blood pressure, weight loss during haemodialysis, haematocrit changes, drug treatment, buffer (acetate or bicarbonate) or presence of diabetes mellitus.

Discussion

Arteriosclerotic complications contribute to a large extent to the morbidity and mortality of chronic haemodialysis patients. While coronary heart disease has received considerable attention [7], peripheral vascular disease has been studied less. Certain correlations between age, smoking and duration of dialysis therapy and accelerated arteriosclerosis have been established [3,19]. Some patients report chest pain and/or leg discomfort during haemodialysis without changes in blood pressure or heart rate. Microcirculatory disturbances, such as dialysis-induced vasodilation, volume depletion, increased viscosity, leukocyte activation, changes in electrolyte homeostasis, release of vasoactive cytokines, reduced NO and others may contribute to the pathogenesis of these symptoms [10,11]. In patients with pre-existing severe PAOD, haemodialysis can lead to a critical reduction in peripheral perfusion, potentially resulting in irreversible tissue damage. The repetitive alteration of microvascular perfusion during haemodialysis could also be a pathogenic factor in the arteriosclerotic process. At present, only few data are

available regarding the perfusion of the microvasculature in patients on maintenance haemodialysis which have shown qualitative and quantitative structural changes [12,14,15,18,20–22]. However, there are no data about the quality of nutritive skin perfusion of the lower extremity in patients with PAOD. Therefore, we investigated the acute effects of haemodialysis on the cutaneous microcirculation in chronic haemodialysis patients with and without PAOD. The measurement of $tcPO_2$ is a sensitive method for studying acute effects of interventions on nutritive skin perfusion in patients with peripheral vascular disease [16–18,23]. In our experimental setup, normal values of $tcPO_2$ at the forefoot are 50–70 mmHg in healthy controls. Recordings of $tcPO_2$ were performed at an electrode temperature of 44°C, which results in a better reproducibility in contrast to measurements at 37°C. Further advantages of the heat-induced hyperaemia of the skin are that the maximum possible local PO_2 values can be evaluated, $tcPO_2$ is less dependent on room temperature, sympathicus activation and blood pressure, and a huge amount of data exists for patients with PAOD [17,24,25].

Total skin blood flow consists of nutritive and thermoregulatory blood flow through A–V shunts and is highly variable; we, however, focused on the quality of nutritive skin perfusion, because in patients with peripheral arterial disease the risk of skin necrosis, wound healing, etc. is dependent on cutaneous oxygen supply.

The results of our study indicate that the cutaneous oxygen supply is diminished during haemodialysis. The decrease in $tcPO_2$ reflects a reduced nutritive cutaneous perfusion irrespective of the presence of PAOD.

The reduced oxygen supply to the skin could be explained by several mechanisms. Arterial PO_2 may decrease by 4–5 mmHg during haemodialysis especially when acetate buffer is used [26,27]. This, however, is an unlikely explanation in the present study since we did not observe a correlation between haemodialysis buffer and fall in $tcPO_2$. Furthermore, a decrease in arterial PO_2 by 5 mmHg will not result in the observed 20% reduction in tissue oxygen supply. In normal skin, $tcPO_2$ reflects PO_2 of arterial blood [28].

A further explanation for the decreased $tcPO_2$ could be that during haemodialysis, cardiac output will not increase adequately due to volume depletion, peripheral vasodilation and altered myocardial compliance [29]. In many patients with end-stage renal disease, the maintenance of cardiac output can be disturbed by autonomic neuropathy and/or antihypertensive medications. Although the decrease in $tcPO_2$ tended to be more pronounced in patients with an extensive fall in blood pressure, using an electrode temperature of 44°C, $tcPO_2$ is reported as being independent of arterial blood pressure over a wide range [25]. No correlation was found between the decrease in $tcPO_2$ and ultrafiltration weight loss, blood pressure, drug treatment or the presence of neuropathy. However, the present study did not have the statistical power to detect nonrandom variations in these parameters.

In addition to changes in central haemodynamics, alterations in microvascular perfusion itself may contribute to the reduced oxygen supply to the skin [10,11]. The mechanisms of the reduced oxygen supply are the subject of further investigations.

The lack of a significant difference in $tcPO_2$ between patients with and without PAOD is unexpected. In patients with intermittent claudication, oxygen supply meets oxygen demand at rest, but cannot meet the increased metabolic demand of exercise [17,23], which can cause a fall in $tcPO_2$ by 50–80% [24]. In contrast to walking, the haemodynamic stress of haemodialysis did not exceed the collateral capacity. The 20% reduction in skin oxygen supply during dialysis did not jeopardize the tissue, because only a $tcPO_2$ below 20–30 mmHg is considered insufficient for tissue survival.

An increase in skin temperature is a known phenomenon during haemodialysis. Temperature changes tended to be smaller in patients with PAOD, but did not reach statistical significance.

To determine microvascular reactivity, we introduced the easily applicable technique of local cooling of the skin. Analogously to the reactive hyperaemia response after arterial occlusion, the time to reach baseline skin temperature can be considered as an indirect measure of vasodilatory capacity. A difference between patients with and without PAOD was recognized when assessing microvascular flow reserve after standardized cooling of the skin. These findings are consistent with a more dilated cutaneous microvascular bed at rest in patients with PAOD than in controls. This technique seems to be more sensitive than the measurement of $tcPO_2$ to detect the disturbance of microvascular perfusion in patients with peripheral vascular disease.

The effects of haemodialysis on cutaneous microcirculation and skin oxygen supply were prolonged but did not reach a critical level in patients with intermittent claudication. In patients with severe PAOD and impending critical limb ischaemia, a further reduction of flow by haemodialysis potentially could precipitate irreversible ischaemic tissue damage.

In conclusion, cutaneous perfusion is impaired during haemodialysis in patients without vascular disease and in patients with intermittent claudication. Oxygen supply to the skin is reduced by 20% in both groups. Hyperaemia after cooling is significantly diminished during dialysis in patients with PAOD. The changes in peripheral perfusion do not compromise oxygen supply critically. However, in patients with severe PAOD, haemodialysis might result in critical flow impairment. These findings are relevant for the treatment of patients with peripheral vascular disease undergoing maintenance haemodialysis.

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