Microvascular Dilatation after Haemodialysis Is Determined by the Volume of Fluid Removed and Fall in Mean Arterial Pressure

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Key Words

Dialysis • End-stage renal failure • Microvasculature • Venules • Nitric oxide

(–0.36, CI –0.72 to –0.01, $p < 0.05$) after adjusting for age, gender, diabetes and dyslipidaemia. **Conclusion:** Haemodialysis is associated with systemic venular dilatation.

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Abstract

Background/Aims: The effects of haemodialysis on the microcirculation are poorly understood. This study examined the changes in small vessel calibre. **Methods:** 24 patients (including 12 males, median age 62.5 years, range 30–87) underwent digital retinal photography immediately before and after routine haemodialysis. Arteriolar and venular calibres were measured from the images by a trained grader using a highly reproducible, computer-assisted method. **Results:** Patients had an average 2.0 ± 0.3 litres of fluid removed with dialysis, and their mean arterial blood pressure fell by 6.8 mm Hg (CI 13.8–0.2, $p = 0.06$). Retinal arteriole calibre did not change (mean difference $2.3 \mu\text{m}$, CI –1.1 to 5.7, $p = 0.17$) but the venules dilated (mean difference $12.7 \mu\text{m}$, CI 7.3–18.3, $p < 0.001$). Calibre returned to baseline by 2 h. Venules dilated less in diabetics than non-diabetics (mean difference $-6.2 \mu\text{m}$, CI –9.6 to –2.9, $p < 0.01$). Retinal venular dilatation correlated positively with the volume of fluid removed per kilogramme body weight (5.9, CI 0.2–11.5, $p = 0.04$), and negatively with the fall in mean arterial pressure

Introduction

Individuals with chronic kidney disease have an increased risk of macrovascular disease, and dialysis patients have a cardiovascular mortality that is 20 times greater than in those with normal renal function [1]. Microvascular disease is also increased in renal failure, and contributes to the greater likelihood of heart failure, stroke, dementia, and progressive renal impairment [2–7]. In renal failure, both ‘traditional’ risk factors, such as hypertension and dyslipidaemia, and ‘non-traditional’ factors, including inflammation, endothelial damage and disturbed calcium-phosphate homeostasis, are believed responsible for the increase in vascular events [8].

The systemic microvasculature can be assessed in vivo by direct examination of the retinal vessels [9]. Retinal changes in microvascular disease include focal and generalised arteriolar narrowing, arteriovenous nicking, haemorrhage and exudates [10–12]. Specialised methods

use quantitative computer-based techniques to measure retinal vessel calibre directly from digital images [13–15], or indirectly, from blood flow using Doppler ultrasonography [16, 17]. Changes in vessel branching patterns or ‘fractals’ that reflect ischemia can also be assessed from digitised retinal images [18, 19].

Patients with renal failure typically have a microvasculature that is damaged by hypertension and dyslipidaemia, and possibly by diabetes and smoking [20–22]. Arterioles become narrower with increasing age, hypertension and atherosclerosis [22]. Venules dilate with systemic inflammation, diabetes, obesity, smoking and dyslipidaemia [23–27]. Both arterioles and venules are narrowed in renal failure, and the more severe the renal failure, the smaller the vessel diameter [28]. However, microvascular calibre is also dynamic, and may be affected by fluid status and vasoactive stimuli [16, 17], but not, in population-based surveys, by commonly-used medications [29].

Patients with end-stage kidney disease who are haemodialysed undergo fluctuations in their fluid status, and levels of electrolytes and uremic toxins, during treatment. Dialysis is sometimes associated with hypotension, headache, nausea, muscle cramps and cardiac ischemia, and while the mechanisms are incompletely understood, changes in the microvascular blood flow have been demonstrated [16, 17].

This study examined the direct effect of dialysis on the calibre of the retinal, and hence systemic, microvasculature and the major determinants of these changes.

Subjects and Methods

Study Participants

Patients undergoing morning haemodialysis 3 times weekly, and 2 days after their previous treatment, at a major metropolitan centre were approached to take part in this study. The only patients who were excluded were those in whom the retina could not be visualised, usually because of cataracts. Haemodialysis was performed using Gambro machines (AK200S; Gambro, Sydney, N.S.W., Australia), HCO₃-based dialysate, at 37°C, ultrapure water and synthetic biocompatible dialysers (Polyflux H; Gambro). Blood flow rates ranged from 200 to 400 ml/min, and ultrafiltration varied according to individual prescription. Anticoagulation was achieved with a 1,000-unit intravenous heparin bolus followed by a 500- to 1,000-unit/h infusion.

Patient medical details, as well as their pre- and post-dialysis weights, and systolic and diastolic blood pressures were recorded.

Retinal Imaging and Grading

Digital retinal imaging was performed before and immediately after dialysis. Photographs centred on the optic discs of

both eyes were recorded with a Canon CR5 non-mydratic retinal camera (Canon, Japan). Retinal vascular calibre was measured using a computer-assisted system (University of Wisconsin, Madison, Wisc., USA) by a trained grader who was masked to participant characteristics [30]. Briefly, all vessels coursing through a zone 0.5–1.0 disc diameters from the disc margin were measured using a computer imaging program (IVAN; University of Wisconsin). Measurements were summarised as the central retinal artery and vein equivalents (CRAE and CRVE, respectively) using the formulae proposed by Knudtson et al. [31]. This method was highly reproducible with intra-class correlation coefficients for CRAE and CRVE of 0.986 and 0.989, respectively.

In addition, CRAE and CRVE were studied pre- and 0, 1, 2 and 18 h post-dialysis in 8 eyes (2 male and 6 female).

Statistical Analysis

Continuous variables were compared with Student's *t* test and dichotomous variables with Fisher's exact test. The CRAE and CRVE before and after dialysis were compared with Student's paired *t* test. The effect of the volume of fluid removed per kilogramme body weight and the number of years on dialysis on the change in vessel calibre were measured with Pearson's correlation coefficient. The determinants of the change in CRAE and CRVE with dialysis were examined in multiple linear regression analysis.

A result was considered significant if the 95% confidence interval did not include 1.00, and the *p* value was <0.05. Statistical analyses were performed using Stata version 10 software (Stata Corp., College Station, Tex., USA).

This study conformed with the Declaration of Helsinki, and was approved by the Human Research Ethics Committees of Austin Health and Northern Health, and all participants provided written, informed consent.

Results

Characteristics of Participants

Twenty-four patients (12 males) with a median age of 62.5 years (range 30–87) were studied. They had end-stage kidney disease from diabetic nephropathy (*n* = 8, 33%), glomerulonephritis (*n* = 4, 17%), renovascular disease (*n* = 5, 21%), reflux nephropathy (*n* = 2, 8%), or from surgery, trauma or nephrotoxic medication (*n* = 5, 21%). Five (21%) had previously undergone renal transplantation and, overall, they had spent a median of 4.5 years continuously (range 0.2–34) on dialysis until now.

Twenty patients (83%) had treated hypertension (systolic/diastolic blood pressure ≥140/90 mm Hg), 10 (42%) had diabetes, 18 (75%) had dyslipidaemia, and, while none smoked currently, 11 (46%) were ex-smokers. Seven (29%) were currently treated with vasodilators (isordil, prazosin or hydralazine) and 1 (4%) with an angiotensin-converting enzyme inhibitor.

Fig. 1. Time course of CRAE (a) and CRVE (b) with dialysis.

Table 1. Changes with dialysis in all patients

Criteria	All dialysis patients (n = 24)		p value mean difference (95% CI)
	pre-dialysis	post-dialysis	
Weight, kg	77.4 ± 17.0	75.4 ± 16.9	<0.001 -2.0 (-2.3 to -1.6)
Systolic BP mm Hg	137.0 ± 20.5	125.5 ± 19.4	0.03 -11.5 (-22.0 to -0.9)
Diastolic BP mm Hg	68.8 ± 16.2	64.4 ± 13.7	0.24 -4.4 (-11.9 to 3.1)
Mean arterial pressure mm Hg	91.5 ± 13.4	84.7 ± 11.5	0.06 -6.8 (-13.8 to 0.2)
CRAE, μm	144.6 ± 13.0	146.9 ± 12.8	0.17 2.3 (-1.1 to 5.7)
CRVE, μm	209.2 ± 24.3	221.9 ± 22.3	0.001 12.7 (7.3–18.0)

Systemic Changes with Dialysis

Immediately after dialysis, the patients' mean body weight fell from 77.4 ± 17.0 to 75.4 ± 16.9 kg which represented $2.6 \pm 1.1\%$ of their total weight (difference -2.0 kg, CI -2.3 to -1.6 , $p < 0.001$) (table 1). Their mean arterial blood pressure fell from 91.5 ± 13.4 to 84.7 ± 11.5 mm Hg (difference -6.8 mm Hg, CI -13.8 to 0.2 , $p = 0.06$), and their mean systolic (difference -11.5 mm Hg, CI -22.0

to -0.9 , $p = 0.03$), but not diastolic, blood pressures fell significantly. However, none of these patients was symptomatic from the fluid removal or fall in blood pressure.

Retinal Vascular Calibre

The patients' mean CRAE did not change significantly after dialysis (144.6 ± 13.0 and 146.9 ± 12.8 μm, difference 2.3 , CI -1.1 to 5.7 , $p = 0.17$). However, their mean CRVE increased from 209.2 ± 24.3 to 221.9 ± 22.3 μm (difference 12.7 , CI 7.3 – 18.0 , $p < 0.001$) (table 1). The CRVE was maximal immediately after dialysis and returned to baseline by 2 h (fig. 1).

Determinants of the Increase in CRVE after Dialysis

After dialysis, the CRVE increased in both males and females (17.9 μm, CI 9.6 – 21.2 , $p = 0.001$, and 7.4 μm, CI 0.8 – 14.0 , $p = 0.03$, respectively), but the increase was greater in males (difference 10.4 μm, CI 7.8 – 13.1 , $p < 0.001$).

Prior to dialysis, the CRVE was also not different between diabetics and non-diabetics (211.4 ± 25.4 and 207.7 ± 24.3 μm, respectively, difference 3.7 μm, CI -17.6 to 25.0 , $p = 0.7$). After dialysis, the CRVE increased in both diabetics (9.0 μm, CI 0.8 – 17.3 , $p = 0.04$) and non-diabetics (15.3 μm, CI 7.6 – 22.9 , $p = 0.001$) but the increase was less in diabetics (difference -6.2 μm, CI -9.6 to -2.9 , $p = 0.001$).

After dialysis, the change in CRVE correlated with the volume of fluid removed per kilogramme body weight (Pearson's correlation coefficient 0.41 , $p = 0.04$) (fig. 2). There was no correlation with the years spent on dialysis (Pearson's correlation coefficient 0.07 , $p = 0.75$).

Independent Determinants of the Increase in CRVE after Dialysis

The increase in CRVE after dialysis was determined by the volume of fluid removed per kilogramme body weight (5.87 , CI 0.0 – 11.5 , $p = 0.04$) and the fall in mean arterial pressure (-0.36 , CI -0.7 to 0.0 , $p = 0.46$) after adjusting for age, gender, diabetes, and dyslipidaemia (table 2).

Discussion

The major findings of this study were that dialysis resulted in dilatation of the retinal venules, and that the dilatation was short-lived. When all possible variables were taken into account, the major determinants of venular dilatation post-dialysis were the volume of fluid removed and the fall in mean arterial pressure.

Although the CRVE after dialysis appeared to increase more in males than females, and less in diabetics than non-diabetics, gender and diabetes were not independent determinants of dilatation. Patients with diabetes typically have larger retinal venules than non-diabetics [26], even in renal failure [28]. In this study, venules in diabetics were only marginally larger than in non-diabetics, and dilated less after dialysis suggesting either that these vessels were already maximally dilated or that they were damaged and less responsive to further stimuli. The more pronounced dilatation in males may have been because fewer were diabetic and because they had more fluid removed.

The major strengths of this study were that it examined a cohort of well-characterized patients who underwent routine dialysis in the same unit contemporaneously. It also used highly reproducible methods to assess changes in retinal vessel calibre. The study's limitations were that the cohort was small, clinically heterogeneous, and included many diabetics, and that the volume of fluid removed varied in individual patients. This nevertheless probably represents a typical cohort for many dialysis units.

Dilatation of the retinal microvasculature after dialysis is thought to occur secondary to the release of vasoactive factors, such as nitric oxide, in response to the reduced intravascular volume [32]. For example, asymmetric dimethylarginine, an inhibitor of nitric oxide synthase, accumulates in renal failure [33, 34], but is removed by dialysis, resulting in enhanced nitric oxide activity and consequent vasodilatation.

Retinal vasodilation reflects systemic changes that mainly affect the capacitance vessels in the bowel and periphery and probably contribute to the hypotension, headache, nausea, muscle cramps and myocardial ischemia that may result from the removal of large volumes of fluid. The time course of post-dialysis venular vasodilation demonstrated here that it was short-lived and that calibre returned to baseline by about 2 h which was consistent with the half-life of the putative vasoactive factors.

Retinal venular dilatation has been described previously after dialysis using colour Doppler ultrasonography and laser Doppler velocimetry [16, 17], but our study measured vessel calibre directly, and assessed the determinants of the vasodilation. Microvascular grading is convenient because it does not require the use of special equipment but only access to a vascular calibre grading centre.

The present study did not demonstrate any change in arteriolar size after dialysis, although generally, arteriolar calibre changes in parallel with venular calibre but to a lesser extent.

Fig. 2. Change in CRVE with fluid removed per kilogramme body weight.

Table 2. Determinants of CRVE change

Criteria	Difference in CRVE		p value
	coefficient	95% CI	
Age	0.15	−0.2 to 0.5	0.37
Gender	2.24	−10.4 to 14.91	0.71
Diabetes	−4.06	−15.6 to 7.5	0.47
Dyslipidaemia	−7.39	−19.6 to 4.8	0.22
Volume removed per kg body weight	5.87	0.2–11.5	0.04*
Difference in mean arterial pressure	−0.36	−0.7 to 0.0	0.046*
Constant	−8.48	−31.2 to 14.3	0.44
Prob >F = 0.04			
* = p significant.			

Studies in other populations have found that retinal venular dilatation predicts an increased risk of cardiac disease or stroke [35, 36], but the dilatation seen after dialysis is transient and serves to improve the local blood supply, while also contributing to dialysis-associated hypotension.

The retinal microvasculature represents a model system in which to further examine dialysis-induced venular dilatation.

Acknowledgements

We would like to thank the many patients who took part in these studies. This work was published as an abstract in the abstract book of the American Society of Nephrology Annual Meeting, November 2010.

Disclosure Statement

The authors have no support or financial disclosures to declare. F.K.N.-F.H.T. and Q.L.O. were medical students who undertook this research as part of their B Biomedical Science studies. The results described here have not been published previously in whole or part except in abstract format.

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