SCIENTIFIC REPORT

Effect of haemodialysis on retinal circulation in patients with end stage renal disease

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Aims: To investigate the effect of haemodialysis on retinal circulation in patients with end stage renal disease (ESRD).

Method: Seventeen consecutive patients with ESRD were recruited into the study. The authors simultaneously measured changes in vessel diameter and blood velocity and calculated the retinal blood flow (RBF) in the retinal veins in patients with ESRD before and after haemodialysis using a laser Doppler velocimetry system. In addition, the relations between the changes in systemic and retinal circulatory parameters were examined.

Results: There was a group averaged increase in vessel diameter ($p=0.003$) after haemodialysis. However, the blood velocity and RBF values obtained after haemodialysis were not significantly different from those before haemodialysis ($p=0.66$ and $p=0.63$, respectively). The changes in vessel diameter were negatively ($r=-0.549$, $p=0.02$) correlated with the change in MABP, but the changes in blood velocity and RBF were positively correlated with the change in MABP ($r=0.683$, $p<0.002$ and $r=0.589$, $p<0.01$, respectively). The change in RBF was also inversely correlated with the increase in haematocrit ($r=-0.693$, $p<0.002$) and the amount of fluid removed ($r=-0.597$, $p<0.01$).

Conclusion: The results indicate that haemodialysis and the associated changes in systemic circulatory parameters may affect the retinal circulation in patients with ESRD.

Recent improvements in the management of patients with end stage renal disease (ESRD), who are dependent on haemodialysis, have led to increased survival.^{1–2} It is important that good visual function is maintained for these patients' quality of life. Ocular vascular diseases such as ischaemic optic neuropathy and retinal vein occlusion, which are well known ocular complications of renal failure and dialysis,^{3–5} may severely impair the visual function in patients with ESRD. Therefore, careful and precise evaluation of the changes in retinal circulation is needed to prevent these vascular disorders and visual function impairment during management of these patients.

Abnormal changes in systemic haemodynamic factors such as hypertension, hypotension after dialysis, and anaemia develop in patients with ESRD.^{6–7} However, the effect of haemodialysis on the retinal circulation has not been evaluated. In the present study, we measured the changes in retinal circulation induced by haemodialysis using a laser Doppler velocimetry system⁸ to investigate the effect of haemodialysis on retinal circulation in patients with ESRD. We also examined the relation between the changes in systemic and retinal circulatory parameters induced by haemodialysis.

METHODS

Subjects

The study included 17 patients (10 men and 7 women; mean age 53.8 (SD 3.7) years, range 24–74 years) with ESRD. All were outpatients at Asahikawa City Hospital (Asahikawa, Japan). The causes of renal failure in the 17 patients included diabetes mellitus (7), chronic glomerulonephritis (4), reflux nephropathy (2), polycystic kidney disease (1), hypotension (1), and unknown factors (n2). All patients were non-smokers and had no evidence of cardiac or cerebrovascular disorders. All had been undergoing regular maintenance haemodialysis for 3–4 hours three times weekly for from three to 96 months (mean 34.3 (SD 6.7) months). Patients continued to take their antihypertensive medications, including angiotensin converting enzyme inhibitors, calcium channel blockers, and β blockers during the study.

All patients had a corrected visual acuity better than 20/40. No ophthalmic surgical procedures were performed. Ten patients without diabetes had no ocular disorders. Seven patients with diabetes had no diabetic retinopathy. Patients with background, preproliferative, or proliferative diabetic retinopathy were excluded.

General procedure

The procedure followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients after the study was fully explained.

Systolic, diastolic, mean arterial blood pressure (MABP), and heart rate were recorded with electrical sphygmomanometry (EP-88Si, Colin, Tokyo, Japan). Intraocular pressure (IOP) was monitored by applanation tonometry (Haag Streit, Bern, Switzerland). Arterial blood samples were obtained before and after haemodialysis for the haematocrit measurement. The pupils were dilated using a combination of 0.5% tropicamide and 1% phenylephrine eye drops.

Haemodialysis

Routine haemodialysis procedures were followed for each patient according to his or her prescription. All patients underwent a single bicarbonate haemodialysis with triacetate hollow fibre dialysers. The blood flow rate ranged from 200–400 ml/min, dialysate flow 500 ml/min, and the ultrafiltration rate varied according to prescription. The dialysate contained: Na⁺ 140 meq/l, HCO₃⁻ 30 meq/l, K⁺ 2.0 meq/l, Cl⁻ 110 meq/l, Ca⁺⁺ 3.0 meq/l, and Mg⁺⁺ 1.0 meq/l. Heparinisation was achieved with a 5000 unit intravenous bolus followed by a 500 units/hour intermittent intravenous bolus.

Measurement of retinal blood flow

A laser Doppler velocimetry system (Canon Laser Blood Flowmeter; CLBF model 100, Canon, Tokyo, Japan) was used

Abbreviations: ESRD, end stage renal disease; IOP, intraocular pressure; MABP, mean arterial blood pressure; NO, nitric oxide; RBF, retinal blood flow; ADMA, asymmetric dimethylarginine.

Table 1 Effects of haemodialysis on systemic haemodynamic parameters and intraocular pressure

Variable	Before haemodialysis	After haemodialysis	p Value
Haematocrit (%)	28.7 (0.7)	31.3 (0.9)	<0.01
SBP (mm Hg)	142.7 (5.7)	124.9 (7.5)	<0.05
DBP (mm Hg)	74.9 (3.7)	69.8 (3.7)	NS
MABP (mm Hg)	97.5 (4.0)	88.2 (4.7)	NS
HR (beats/min)	84.5 (3.4)	86.9 (4.8)	NS
IOP (mm Hg)	12.1 (0.6)	11.6 (0.6)	NS
Body weight (kg)	55.3 (2.5)	53.3 (2.4)	<0.01
Fluid removed (litres)		1.9 (0.2)	

Values are expressed as mean (SE).

SBP, systolic BP; DBP, diastolic BP; MABP, mean arterial blood pressure; HR, heart rate; IOP, intraocular pressure; NS, not significant.

to estimate retinal blood flow (RBF). We recently described this system,^{8,9} which allows non-invasive measurement of absolute values of the red blood cells flowing in the centre line of the retinal vessel, based on bidirectional laser Doppler velocimetry.¹⁰ This device includes the vessel diameter measurement system and the vessel tracking system.^{8,9} The RBF was calculated according to the following formula:

$$\text{RBF} = V \times \text{Area}/2$$

where V is the time average of the centre line blood speed during the cardiac cycle, and Area is the cross sectional area of the retinal vessel at the laser Doppler measurement site.^{11,12} Measurement sites were generally between the disc margin and the first bifurcation.

Study protocol

All patients were studied under the same conditions 30 minutes before and after dialysis. Using the laser Doppler velocimetry system, five continuous measurements of each parameter were obtained every minute for 5 minutes at a single site along a major temporal retinal vein in one eye of each patient, and the mean of the five measurements was defined as the value. Systemic and ocular haemodynamic parameters were measured simultaneously.

Statistical analysis

All values are expressed as the mean (standard error). The values before and after haemodialysis were compared with paired *t* tests. Correlations between variables were analysed using Pearson's correlation model and linear regression analysis; *p* values less than 0.05 were considered statistically significant.

RESULTS

Except for the haematocrit, values remained within the normal range (table 1). The haematocrit, which was very low before dialysis, significantly increased whereas body weight and systolic BP significantly decreased after haemodialysis. The changes in these values induced by dialysis reverted toward normal levels.

The averaged coefficients of variation of diameter, velocity, and RBF in a retinal vein of five baseline measurements obtained from all patients in this study were 5.2 (SE 0.8), 12.9 (SE 1.2), and 17.2 (SE 1.9)%, respectively. Figure 1 shows the changes in the retinal haemodynamic parameters induced by haemodialysis in all patients. The average retinal vessel diameter increased significantly ($p < 0.01$) from 115.9 (SE 3.7) to 120.3 (SE 3.6) μm (fig 1A) after haemodialysis. On the other hand, retinal blood velocity and RBF changed from 29.7 (SE 2.2) mm/s to 28.5 (SE 2.8) mm/s and from 9.6 (SE 1.0) to 10.0 (SE 1.3) $\mu\text{l}/\text{min}$, respectively. In contrast to the change in diameter, the overall changes in blood velocity and RBF did not achieve statistical significance, probably because of the large individual differences (fig 1B and C).

Relation between changes in systemic and retinal circulatory parameters

The change in vessel diameter was significantly negatively correlated ($r = -0.549$, $p = 0.02$; fig 2A), but the changes in blood velocity and RBF were positively correlated ($r = 0.683$, $p < 0.002$; $r = 0.589$, $p < 0.01$; fig 2B and C, respectively) with the change in MABP. In addition, the change in RBF was negatively correlated with the amount of fluid removed by dialysis ($r = -0.597$, $p < 0.01$) (fig 3A) and the change in haematocrit ($r = -0.693$, $p < 0.002$) (fig 3B). There was also a negative correlation between the changes in haematocrit and MABP ($r = -0.59$, $p < 0.02$) and positive correlation between the changes in haematocrit and the amount of fluid removed by haemodialysis ($r = 0.708$, $p < 0.001$).

DISCUSSION

The group averaged values of vessel diameter after haemodialysis significantly increased compared with those obtained before haemodialysis (fig 1A). To our knowledge, vasodilation after haemodialysis has never been found in retinal vessels. The plasmatic accumulation of vasoactive substances such as adrenomedullin¹³ and nitric oxide (NO)¹⁴ have recently been reported. In addition, recent studies have reported that asymmetric dimethylarginine (ADMA), an inhibitor of NO synthase, accumulates in renal failure and reduces after haemodialysis, resulting in the enhancement of the NO activity.^{15,16} These changes in vasoactive substances would lead to vasodilation. Although we did not measure the

Figure 1 Plots show changes in (A) vessel diameter, (B) blood velocity, and (C) RBF in the retinal veins of all patients. RBF, retinal blood flow; NS, not significant.

Figure 2 Relation between the change in MABP and (A) vessel diameter ($r = -0.549$, $p = 0.02$), (B) blood velocity ($r = 0.683$, $p < 0.002$), and (C) RBF ($r = 0.589$, $p < 0.01$). MABP, mean arterial blood pressure.

serum level of vasoactive substances in the present study, we speculate that the dilation of retinal vessel after haemodialysis observed in the present study might be caused by the increase in vasodilative substances. Further studies are required to measure the concentration of these vasoactive substances and clarify their role in the change in retinal circulation induced by haemodialysis.

In contrast to the increase in diameter after haemodialysis, the group averaged changes in blood velocity and RBF were not statistically significant (fig 1B and C). These results indicate that the changes in MABP have large individual differences in our patients with ESRD and may greatly affect the changes in blood velocity and RBF induced by haemodialysis. In addition, our results showing that changes in both velocity and RBF were positively correlated with the change in MABP (fig 2) suggest that the change in RBF is mainly dependent on the change in blood velocity, whereas the increase in diameter has little effect on the net change in RBF.

In addition to the positive correlation between MABP and RBF, there was a significant negative correlation between both the changes in haematocrit and RBF (fig 3A) and the amount of fluid removed and the change in RBF (fig 3B). The former negative correlation seems to be similar to that demonstrated between the haematocrit and cerebral blood flow in patients on haemodialysis.^{17,18} Although those results were obtained from another vascular bed, those reports are in good agreement with ours. We could not provide a definitive explanation for these two associations, but it is reasonable to consider that the change in haematocrit and the amount of fluid removed could affect blood flow by an alteration in the viscosity of whole blood, which is important in determining the blood flow. Following Poiseuille's law, the blood flow varies inversely with viscosity, suggesting that increased viscosity leads to increased vascular resistance and decreased blood flow.¹⁹ In addition, the viscosity of whole blood increases as the haematocrit increases.^{19,20} Although we did

not measure blood viscosity, the significant increase in haematocrit would cause the rise in viscosity and vascular resistance, resulting in decreased RBF.

There were several limitations in our study. Firstly, we should take care in the interpretation of our results because patients with several underlying diseases were included in the present study. Because the number of patients was small in our study, we could not perform the analysis by multiplying subgroups of patients. However there were no differences in the changes in vessel diameter, blood velocity, and RBF induced by haemodialysis between diabetic patients ($n = 7$) and the other patients ($n = 10$) (data not shown). Secondly, the relation between RBF and retinal red blood cell flux should be considered using bidirectional laser Doppler technique. However, the observed increase in haematocrit by haemodialysis does not seem to alter this relation, because a laser Doppler output signal was insensitive to haematocrit variations in the range of 16–44% in an in vitro tube.²¹

In conclusion, our results indicate that haemodialysis and the associated changes in systemic circulatory parameters—that is, systemic BP, haematocrit, and the amount of fluid removed—could affect the retinal circulation in ESRD patients. Further study is needed to clarify the clinical significance of the haemodialysis associated changes in retinal circulation.

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Figure 3 Relation between the change in RBF and the fluid removed by haemodialysis (A) ($r = -0.597$, $p < 0.01$) and the increase in haematocrit (B) ($r = -0.693$, $p < 0.002$). Fluid removed, the amount of fluid removed by haemodialysis. Ht, haematocrit.

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