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Effect of Normalization of Hematocrit on Brain Circulation and Metabolism in Hemodialysis Patients

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Abstract. Full correction of anemia with recombinant human erythropoietin (rhEPO) has been reported to reduce the risk of cardiovascular morbidity and mortality and improve the quality of life in hemodialysis (HD) patients. Effects of normalization of hematocrit on cerebral blood flow and oxygen metabolism were investigated by positron emission tomography. Regional cerebral blood flow (rCBF), cerebral blood volume (rCBV), oxygen extraction ratio (rOER), and metabolic rate for oxygen ($rCMRO_2$) were measured in seven HD patients before and after correction of anemia and compared with those in six healthy control subjects. In addition, blood rheology before and on rhEPO therapy was measured in HD patients, which included blood viscosity, plasma viscosity, erythrocyte fluidity, and erythrocyte aggregability. The results showed that plasma viscosity was high (1.51 ± 0.19 mPa · s) and erythrocyte fluidity was low (85.8 ± 4.8 $Pa^{-1} \cdot s^{-1}$), while whole blood viscosity was within the normal range (3.72 ± 0.38 mPa · s) before rhEPO therapy. After treatment, the hematocrit rose significantly from 29.3 ± 3.3 to $42.4 \pm 2.2\%$ ($P < 0.001$), accompanied by a significant increase in the whole blood viscosity to 4.57 ± 0.16 mPa · s, nonsignificant decrease in erythrocyte fluidity to 79.9 ± 7.4 $mPa^{-1} \cdot s^{-1}$ and nonsignificant change in plasma viscosity (1.46 ± 1.3 mPa · s). Positron emission tomography measurements revealed that by normalization of hematocrit, rCBF significantly decreased from 65 ± 11 to 48 ± 12 ml/min per 100 cm^3 ($P < 0.05$). However, arterial oxygen content (caO_2) significantly increased from 5.7 ± 0.7 to 8.0 ± 0.4 mmol/L ($P < 0.0001$), rOER of the hemispheres significantly increased from 44 ± 3 to $51 \pm 6\%$ ($P < 0.05$) and became significantly higher than healthy control subjects ($P < 0.05$). In addition, rCBV significantly increased from 3.5 ± 0.5 to 4.6 ± 0.6 ml/100 cc brain tissue. The results showed that oxygen supply to the brain tissue increased with normalization of hematocrit, but it was accompanied by increased oxygen extraction in the brain tissue. This may be assumed to be related to the decrease of erythrocyte velocity in the cerebral capillaries as a result of the decreased blood deformability and the increased plasma viscosity.

Correction of anemia in hemodialysis (HD) patients with recombinant human erythropoietin (rhEPO) results in reduction of the cardiovascular morbidity and mortality by decreasing cardiac output and the left ventricular mass (1). Improvement of exercise capacity, manifested by an increase in oxygen consumption and maximal work load and a decrease in the anaerobic threshold, have also been reported (2). In addition, rhEPO therapy leads to improvement in the quality of life, suggesting that the cognitive deficit resulting from anemia and uremic brain dysfunction is improved (3).

At present, many dialysis centers set the target hemoglobin levels at 10 to 12 g/dl, and numerous clinical trials have shown that achievement of this level of hemoglobin is associated with a significant relief of symptoms and a decrease in the transfusion rate (4).

There is little doubt that fear of access clotting (5), the hypertensinogenic effect of EPO that is probably related to loss of anemic vasodilation (6), and cost considerations have tempered the ambitions of most nephrologists for full correction of hemoglobin (Hb). However, failure of cardiac abnormality to completely regress with only partial correction of anemia has given reason for concern about these subnormal target Hb levels. In addition, rhEPO-related hypertension and access clotting do not exhibit a clear dose-dependent relationship, suggesting the possibility of a threshold, above which no additional excess of these side effects would be expected (7). Some nephrologists were therefore enthusiastic to normalize the Hb value to 14 g/dl. Studies examining the effect of normalization of hemoglobin for patients with end-stage renal failure are still in progress.

In this study, the effects of normalization of hematocrit (Hct) and the related change in blood rheology on the brain circulation and oxygen metabolism were investigated by the positron emission tomography (PET) technique.

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Materials and Methods

Patients

The study comprised patients at the hemodialysis ward who met the following inclusion criteria: (*1*) anemia of renal origin with a baseline Hb concentration <12 g/dl in men and <11 g/dl in women; and (*2*) presence of adequate iron stores, s-ferritin ≥50 μg/L. The exclusion criteria were: (*1*) uncontrolled hypertension (diastolic BP >110 mmHg); and (*2*) coexisting major disease, *e.g.*, liver or cardiac insufficiency, malignancy, etc. Patients selected according to the above criteria were consecutively approached and informed consent was obtained.

Seven hemodialysis patients participated, including five men and two women ranging in age from 49 to 65 yr. They were dialyzed for 4 h three times a week for a period of 2 to 6 yr. The general characteristics of the patients and the etiology of the renal failure are presented in Table 1. All concurrent therapies were accepted, and all of the patients were on different regimens of antihypertensive medication. Oral iron supplementation was given to maintain serum transferrin saturation ≥20 and s-ferritin ≥50 μg/L.

The control group consisted of six healthy subjects who were not on any kind of medication (four men and two women; mean age 53 ± 6 yr [range, 48 to 61 yr]). The study was approved by both the Ethics and Isotopic committees of Uppsala University.

rhEPO Administration

The starting dose of rhEPO (Eprex, Cilag, Sollentuna, Sweden) was 75 IU/kg body wt, given 1 to 3 times per week subcutaneously. The efficacy of the response was determined by the increase in Hb ≥20 g/L compared with baseline observed within 4 wk after the initiation of rhEPO therapy.

If no proper response was achieved, the dose was increased. If Hb had increased and had reached the target level (14 to 15 g/dl for men and 13 to 14 g/dl for women), the EPO dose was lowered and Hb was checked weekly until it became stable.

Three of the seven patients were on long-term treatment with EPO when they were recruited for the study, and their anemia was undercorrected. However, their Hb levels were stabilized for at least 2 mo.

Procedures

The patient was examined on the second day of the dialysis session. After bed rest for 20 min, central hemodynamic variables were measured by transthoracic bioimpedance (NCCOM3; BoMed Medical Manufacturing Ltd., Irvine, CA), which included cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), and mean arterial BP (MAP). Venous blood samples were drawn for estimation of blood rheologic variables and for measurements of plasma fibrinogen and total serum cholesterol.

Table 1. General characteristics and original renal disease of the hemodialysis patients

Patient	Gender	Age (yr)	Original Renal Disease
1	F	58	Chronic glomerulonephritis
2	M	65	Nephrosclerosis
3	M	51	Cardiolipin antibody syndrome
4	F	64	Diabetic nephropathy
5	M	60	IgA nephritis
6	M	50	Diabetic nephropathy
7	M	49	Chronic glomerulonephritis

The patient was transferred in a mobile chair to the Uppsala University PET Center and placed in a supine position in bed in the dimmed PET scanning room. The radial artery was cannulated for blood gas analysis and for measuring the radioactivity in the blood. The brain was scanned in sections parallel to the orbito-meatal line, and the regions of interest (ROI) were set to the bilateral cerebral cortical areas (frontal, temporal, parietal, and occipital cortices), white matter, deep gray matter (striatum and thalamus), and cerebellar cortices.

All of the above measurements were performed at the basal value of Hb before rhEPO therapy and then repeated after the anemia had been corrected and the target Hb level had been stable for 2 mo to achieve a circulatory steady state.

Plasma fibrinogen was measured by a nephelometer (Behring Werke, Vienna, Austria), and cholesterol by an autoanalyzer (Tecnichon, Tarrytown, NY).

Description of the PET Technique

The PET camera (GEMS 2048–15B; General Electric Medical Systems) is equipped with eight rings of 256 detectors each, producing 15 axial tomographic slices which cover 10 cm along the longitudinal axis of the subject, with a spatial resolution of some 6 mm within sections and a spacing of 6.5 mm between sections, measured as full width at half maximum. Images were reconstructed to a 128 × 128 matrix with a pixel (picture element) size of 2 × 2 mm, using a 6-mm Hanning filter. Attenuation correction was based on transmission scans with a $^{68}Ga/^{68}Ge$ rotating pin radiation source.

In the present study, the regional cerebral blood volume (rCBV), cerebral blood flow (rCBF), and the fraction of oxygen in arterial blood extracted by the brain (rOER) along with cerebral metabolic rate of oxygen ($rCMRO_2$) have been measured by means of ^{15}O-labeled carbon monoxide ($C^{15}O$), water ($H_2{}^{15}O$), and oxygen ($^{15}O_2$), respectively. The short half-life of ^{15}O (2.05 min) permits measurements to be made in sequence with about 10 min between successive tracers, resulting in a total study time of 40 to 50 min.

The high affinity binding of $C^{15}O$ to Hb effectively makes $C^{15}O$ a marker of erythrocytes. By relating the concentration of $C^{15}O$ in the brain (as measured by the PET camera) to that in peripheral blood samples, rCBV can be determined, taking into account differences in hematocrit between peripheral blood samples and smaller blood vessels in the brain, using a value of brain/peripheral blood equal to 0.70 (8).

The $H_2{}^{15}O$ molecule is considered to be freely diffusible across the blood-brain barrier, and the initial time dependence of the $H_2{}^{15}O$ concentration in the brain after a bolus injection is essentially determined by the blood flow. Hence, measurement of the time course of the $H_2{}^{15}O$ concentration in the brain and in arterial blood (input function) allows rCBF to be calculated by means of an autoradiographic method. A predefined value of the distribution volume of water in the brain (0.95 ml/cm^3) and an integration time of 60 s were used. The time course of the arterial input function of $H_2{}^{15}O$ to the brain was corrected for delay and dispersion relative to the time course obtained from the radial artery, by nonlinear fitting to the total count rate of the scanner (9).

During continuous inhalation of $^{15}O_2$ in air, steady state will be reached, owing to the equilibration between supply and radioactivity decay of $^{15}O_2$. The metabolism of $^{15}O_2$ results in the formation of circulating labeled water ($H_2{}^{15}O$). Thus, the tissue concentration of $^{15}O_2$, as measured by the PET camera, includes a blood flow-depen-

dent component. However, this may be calculated and accounted for using values of rCBF obtained from the separate blood flow measurement and the content of $H_2{}^{15}O$ in arterial blood during $^{15}O_2$ inhalation. In tissues void of oxygen stores (*e.g.*, oxymyoglobin), the remaining $^{15}O_2$ is determined by the balance between the extraction of $^{15}O_2$ from the blood and the immediate production of $H_2{}^{15}O$ and its clearance from tissues by blood flow. This allows rOER to be obtained, and thus, considering the values of rCBF and the arterial content of oxygen, $rCMRO_2$ can be calculated (10).

Definition of ROI

ROI were delineated bilaterally in axial tomographic sections that were parallel to the orbito-meatal line. The putamen and thalamus were delineated in a single section as regions measuring 1.0 and 1.5 cm^2, respectively. Parietal (three sections) and frontal (two sections) cortical ROI were defined as 10-mm-wide strips of cortex, and obtained as adjacent axial sections cranial to the basal ganglia. The cerebellar cortex ROI was defined as a 10-mm strip covering the periphery of the cerebellum. ROI of the temporal cortex were outlined in two frontal sections (8 mm apart), using 7-mm-wide strips covering the periphery of the cerebellum. The temporal cortex ROI were defined in two frontal sections (8 mm apart), using a 7-mm-wide strip covering the periphery of the temporal lobe. The occipital lobe ROI were represented by 10-mm-wide strips covering the highest blood flow in two adjacent axial sections.

Blood Gas Analyses

Arterial blood gas analyses were performed simultaneously with the PET measurements, using the blood gas analyzer Radiometer ABL 520 (Copenhagen, Denmark). The measurements included blood pH, arterial CO_2 tension (PCO_2), arterial O_2 tension (PO_2), arterial O_2 saturation (SaO_2), arterial O_2 content (caO_2), carboxyhemoglobin, and methemoglobin.

Blood Rheology

All blood samples for rheologic studies were taken with minimal stasis from the antecubital vein into tubes coated with heparin and tested within half an hour. The hemorheologic variables, including whole blood viscosity, plasma viscosity, erythrocyte fluidity, and erythrocyte aggregability, were assessed at 37°C in a low shear rotational viscometer (Contraves AG, Zürich, Switzerland). Plasma viscosity was analyzed at a shear rate of 38 s^{-1} and apparent whole blood viscosity at 100 s^{-1} at native hematocrit.

Erythrocyte aggregation tendency was analyzed as whole blood viscosity at a shear rate of 1 s^{-1}, and corrected for plasma viscosity and the hematocrit (11).

Erythrocyte fluidity, a measure of erythrocyte deformability, was measured by bulk viscometry at a low shear rate (1.0 s^{-1}) as the reciprocal apparent viscosity. The erythrocytes were washed and resuspended to a hematocrit of 55% in isotonic phosphate-buffered saline at pH 7.4 (11).

Evaluating Measurements

Full blood count indices, including Hb concentration, Hct, mean cell volume, and mean cell hemoglobin concentration, were evaluated every second week in a Technicon (Basingstoke, United Kingdom) automated blood cell analyzer for up to 6 mo of treatment. In addition, S-iron, S-transferrin, and S-ferritin were measured by routine clinical laboratory techniques, and complete clinical and physical examinations were performed. Serum aluminum and plasma parathyroid hormone were measured monthly by flameless atomic absorption spectrometry and by RIA, respectively.

Statistical Analyses

The data are expressed as means ± SD. The levels of significance were computed using the conventional *t* test. The two-tailed *t* test for paired data was used for comparisons of measurements before and after dialysis in uremic patients, whereas that for unpaired data was used for comparison of measurements between patients and healthy control subjects. Comparisons with the correspondent nonparametric tests gave the same levels of significance. A P value of <0.05 with both *t* test and the nonparametric test was considered significant, and differences shown to be significant by one test only were considered nonsignificant. Linear regression analysis was performed according to the least squares method.

Results

Hb and Hct rose significantly ($P < 0.001$) from 9.8 ± 1.3 to 14.2 ± 0.6 g/dl and from 29.3 ± 3.3 to 42.4 ± 2.2%, respectively. These increases were achieved over a period of 5 to 6 mo.

With normalization of the Hb level, cardiac output decreased significantly from 5.99 ± 1.21 to 4.32 ± 1.16 L/min ($P < 0.01$) and stroke volume from 79 ± 11 to 64 ± 10 ml ($P < 0.01$) (Table 2). MAP did not change significantly, although there was a significant increase in TPR from 2635 ± 907 to 3632 ± 1 058 dyn · s · cm^{-5} · m^{-2} ($P < 0.05$). None of the patients required adjustment in antihypertensive treatment.

Arterial blood pH, PaO_2, SaO_2, and $PaCO_2$ were not significantly altered by rhEPO treatment (Table 3). The arterial oxygen content increased significantly from an initial value of 5.7 ± 0.7 to a value of 8.0 ± 0.4 mmol/L after correction of anemia ($P < 0.0001$).

The rheologic measurements are presented in Table 4. Whole blood viscosity increased significantly after correction of anemia from 3.72 ± 0.38 to 4.57 ± 0.16 mPa · s ($P < 0.05$)

Table 2. Hemodynamic measurements before and after correction of anemia in uremic patients[a]

	CO (L/min)	SV (ml)	TPR (dyn · s · cm^{-5} · m^{-2})	MAP (mmHg)
Before	5.99 ± 1.21	79 ± 11	2635 ± 907	102 ± 19
After	4.32 ± 1.16[b]	64 ± 10[b]	3632 ± 1058[c]	105 ± 16
Reference value	5 ± 0.5	70 ± 10	2120 ± 460	92 ± 8

[a] CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; MAP, mean arterial pressure.
[b] $P < 0.01$, compared with pretreatment values.
[c] $P < 0.05$, compared with pretreatment values.

Table 3. Arterial blood gas analysis in uremic patients before and after EPO treatment[a]

	pH	PCO_2 (kPa)	PO_2 (kPa)	SaO_2 (%)	caO_2 (mmol/L)	Hb (g/dl)	COHb (%)	MetHb (%)
Before	7.41 ± (0.03)	4.85 ± 0.44	9.10 ± 1.96	94.0 ± 2.9	5.7 ± 0.7	9.8 ± 1.3	2.8 ± 1.0	0.8 ± 0.2
After	7.41 ± (0.03)	4.88 ± (0.56)	9.81 ± (0.61)	94.6 ± (1.1)	8.0[b] ± (0.4)	14.2[b] ± (0.6)	3.0 ± 0.8	0.9 ± 0.2
Reference value	7.40 ± (0.05)	5.30 ± (0.50)	10.50 ± (0.50)	95 ± (3)	8.3 ± (0.3)	M15 ± 1 F14 ± 1	2.25 ± 0.75	1.5 ± 0.5

[a] EPO, erythropoietin; PCO_2, arterial CO_2 tension; PO_2, arterial O_2 tension; SaO_2, arterial O_2 saturation; caO_2, arterial O_2 content; Hb, hemoglobin; COHb, carboxyhemoglobin; MetHb, methemoglobin.

[b] $P < 0.001$, compared with pretreatment values.

(reference value 3.9 to 5.8 mPa · s). There was no significant change in plasma viscosity, but both the pre- and posttreatment values (1.51 ± 0.19 and 1.46 ± 0.13 mPa · s, respectively) were higher than the reference value (1.17 to 1.31 mPa · s). Erythrocyte fluidity decreased nonsignificantly from 85.8 ± 4.8 to 79.9 ± 7.4 $Pa^{-1} \cdot s^{-1}$, and both values were below the normal reference value (101 to 134 $Pa^{-1} \cdot s^{-1}$).

Table 5 presents the values for rCBF, rCBV, rOER, and $rCMRO_2$ in different regions of the brain, including the hemispheres, the cerebellum, the deep nuclei (thalamus and putamen), and the white matter, in HD patients and healthy control subjects. The following description of the results will be limited to the hemispherical cortices, since the behavior in the other brain areas was more or less similar to that in the cortices. The basal hemispheric rCBF was significantly greater in HD patients than in the control group, namely 65 ± 11 and 51 ± 9 ml/min per 100 ml, respectively ($P < 0.05$), whereas rCBV did not differ significantly between the two groups (3.5 ± 0.5 *versus* 3.6 ± 0.8 ml/100 ml brain tissue, respectively). However, there was a disparate response to the normalization of Hb value (Figure 1, A and B). At the same time as rCBF decreased significantly to 48 ± 12 ml/min per 100 ml ($P < 0.05$), rCBV increased significantly to 4.6 ± 0.6 ml/100 ml brain tissue ($P < 0.05$). The posttreatment value of rCBF was not significantly different from that of the healthy control subjects, whereas the posttreatment rCBV value was significantly higher ($P < 0.05$). The cerebral hemodynamic perfusion reserve, which is represented by the ratio of rCBF/rCBV, decreased significantly in HD patients from 18.2 ± 3.0 to 11.3 ± 2.3 ($P < 0.01$), whereas it was 14.5 ± 3.3 in healthy control subjects, a value not significantly different from the pre- and posttreatment values in HD patients.

A significant correlation was found between hematocrit and rCBF ($r = -0.87$, $P < 0.001$) in HD patients, but a less significant correlation was detected between the caO_2 and rCBF ($r = -0.68$, $P < 0.05$) (Figure 2, A and B). In addition, the rOER correlated significantly with the degree of erythrocyte fluidity ($r = -0.6$, $P < 0.05$) and with the ratio of rCBF/rCBV ($r = 0.72$, $P < 0.05$) (Figure 3, A and B).

The pretreatment value for cortical rOER in HD patients (44 ± 3%) did not differ significantly from the value in healthy control subjects (43 ± 4). When the anemia was fully corrected, rOER had increased to 51 ± 6%, a value significantly higher than the pretreatment value and the value in healthy control subjects ($P < 0.05$ for both). On the other hand, cerebral oxygen delivery (a product of rCBF × caO_2) increased significantly from 354 ± 67 to 391 ± 84 ml/min per 100 ml ($P < 0.01$).

The basal cortical $rCMRO_2$ was 3.86 ± 0.60 ml/min per 100 ml in HD patients and was slightly increased after rhEPO therapy to 4.01 ± 0.77 ml/min per 100 ml. Both values were significantly lower ($P < 0.05$) than the value of 5.03 ± 0.68 ml/min per 100 ml in healthy control subjects, but there were no significant differences between corresponding values in other brain regions.

Table 4. Blood rheology measurements before and after correction of anemia[a]

	B-Viscosity ($mPa \cdot s^{-1}$)	P-Viscosity ($mPa \cdot s^{-1}$)	E-Fluidity ($Pa^{-1} \cdot s^{-1}$)	E-Aggregability	Hematocrit (%)
Before	3.72 ± 0.38	1.51 ± 0.19	85.8 ± 4.8	1.2 ± 0.1	29.3 ± 3.3
After	4.57 ± 0.16[b]	1.46 ± 0.13	79.9 ± 7.4	1.22 ± 0.02	42.4 ± 2.2[c]
Reference values	4.8 ± 0.9	1.31 ± 0.07	122 ± 10	1.0 ± 0.10	M:45 ± 2 F:42 ± 2

[a] B, blood; P, plasma; E, erythrocyte.
[b] $P < 0.05$, compared with pretreatment values.
[c] $P < 0.001$, compared with pretreatment values.

Blood Chemistry

Serum aluminum was within the normal range both before and after correction of anemia (6.3 ± 2.2 and 7.5 ± 2.4 μg/L, respectively), and the two values did not differ significantly. Plasma parathyroid hormone was significantly higher after than before rhEPO treatment (84 ± 11 and 54 ± 13 pmol/L, respectively; $P < 0.05$), but both values were higher than normal.

Plasma fibrinogen and serum total cholesterol were elevated in HD patients without any remarkable change related to rhEPO therapy. The fibrinogen values were 6.55 ± 1.38 and 6.10 ± 1.03 g/L before and after rhEPO treatment, respectively, and the serum total cholesterol values were 7.37 ± 1.04 and 6.39 ± 1.13 mol/L.

Discussion

Cardiac output is normally regulated by the interactions of venous return (preload), resistance to outflow (afterload), and myocardial contractility. The hemodynamic response to chronic anemia in our group of HD patients was similar to that reported by others (12,13). There was an increase in the cardiac output, mainly due to an increase in stroke volume, and a decrease in blood viscosity leading to reduction in total peripheral resistance. Apart from the increase in TPR, cardiac output and stroke volume attained values within the normal range after normalization of Hb. MAP did not significantly increase and there was no need to adjust the antihypertensive medication, although TPR was significantly raised. This was probably due to the decrease in the cardiac output.

SaO_2 was within the normal range in the anemic state and did not change significantly with normalization of the Hb level, and the same was true for other Hb compounds, *e.g.*, methemoglobin and carboxyhemoglobin. Correction of anemia led to a significant increase in caO_2, which was within the normal range after treatment. It is known that to enhance gas exchange of the flowing blood, there should be an intracellular convection within the erythrocytes related to their deformability properties and to rotation of the red cell membrane around the cell interior (14). Motthaghy *et al.* (15) found that rigidification of the erythrocyte membrane with diamide, which prevents elongation of the erythrocytes and the concomitant intracellular convection under shear forces, is closely paralleled by a reduction of O_2 uptake. However, the decreased deformability of erythrocytes in our patient group did not affect the Hb oxygen saturation.

At rest, the brain, which constitutes only 2% of the total body weight, receives 15% of the cardiac output of blood and consumes 25% of the total oxygen consumption. There are essentially no stores of oxygen in the brain, and all oxygen extracted from the blood is metabolized (16). In the present study, the hemispherical $CMRO_2$ in the uremic patients was significantly lower than that in the healthy control subjects, both before and after EPO treatment, a finding that has also been reported in another study (17). The reason might be attributable to the actions of some uremic toxins, which could decrease the respiration of mitochondria and induce mitochondrial degeneration (18,19).

It has been reported that rCBF increases with increased cerebral function and metabolism, a process that is called coupling mechanism, and also in case of tissue hypoxia, *e.g.*, anemic hypoxia (20). During anemia, rCBF is significantly higher than that in healthy control subjects to compensate for the reduction in the capacity of the blood to carry oxygen to the brain. The increase of rCBF is achieved through an increase in cardiac output and redistribution of blood to the more vital organs (brain and heart) at the expense of other organs, *e.g.*, the intestine, liver, kidney, and spleen (21).

After normalization of Hb, the rCBF decreased significantly in the HD patients, and this was also reported in another study after partial correction of hematocrit (22). In this study, there was a highly significant correlation between rCBF and hematocrit and a lesser degree of significance with caO_2. Two studies reported that caO_2 appears to be of fundamental importance in the regulation of CBF in humans (23,24), since it is considered a critical determinant of the total amount of oxygen released into the tissues and the tissue pO_2. This contradiction to our study may indicate that the increase in hematocrit may not be associated with a correspondent increase of the tissue pO_2.

The rCBV is of interest in the evaluation of cerebrovascular abnormality because it reflects the vasodilation in response to a decrease in perfusion pressure (25). In healthy control subjects, rCBV is positively related to rCBF, indicating that the vascular space is larger where tissue perfusion is high (26). The rCBF depends on the cerebral perfusion pressure (CPP), which is the difference between the systemic arterial pressure and the venous pressure at the exit from the subarachnoid space (27).

Table 5. The rCBF, rCBV, rOER and $rCMRO_2$ in uremic patients before and after rhEPO therapy compared to healthy control subjects[a]

	Cerebellum	Deep Nuclei		Cerebral Cortices				White Matter	Total Cortices
		Putamen	Thalamus	Parietal	Frontal	Occipital	Temporal		
rCBF ($ml \cdot min^{-1} \cdot 100\ ml^{-1}$)									
before	76 ± 12[b]	87 ± 16[b]	94 ± 15[b]	65 ± 11[b]	56 ± 13	78 ± 13[b]	51 ± 11[b]	29 ± 7	65 ± 11[b]
after	56 ± 11[c]	61 ± 14[d]	66 ± 18[d]	51 ± 13[e]	46 ± 11[e]	61 ± 15[e]	36 ± 9[e]	26 ± 6	48 ± 12[e]
normal	60 ± 11	65 ± 12	71 ± 14	51 ± 9	53 ± 9	64 ± 9	39 ± 8	23 ± 3	51 ± 9
rCBV (ml/100 cc brain tissue)									
before	3.7 ± 0.9	3.1 ± 0.6	2.9 ± 0.7	3.5 ± 0.1	2.6 ± 0.2	4.6 ± 0.8	3.3 ± 0.5	1.3 ± 0.1	3.5 ± 0.5
after	4.8 ± 0.9[e]	3.7 ± 0.8[b,e]	4.8 ± 0.9[b,d]	4.4 ± 0.5[b,e]	3.5 ± 0.4[e]	5.8 ± 0.8[b,c]	4.1 ± 0.4[b,c]	1.7 ± 0.2[b,e]	4.6 ± 0.6[b,c]
normal	4.1 ± 1.1	2.6 ± 0.5	3.7 ± 0.8	3.6 ± 0.7	3.1 ± 0.8	4.6 ± 0.9	3.1 ± 0.7	1.2 ± 0.3	3.6 ± 0.8
rOER (%)									
before	44 ± 3.0	44 ± 7.0	37 ± 9	45 ± 3	43 ± 2	42 ± 3	45 ± 5	40 ± 4	44 ± 3
after	50 ± 2.0[b,e]	55 ± 3.0[c,f]	40 ± 5	52 ± 6[b,e]	50 ± 6[b,e]	48 ± 6	52 ± 5[e,f]	47 ± 2[b,e]	51 ± 6[b,e]
normal	43 ± 3.0	43 ± 8.0	39 ± 3	44 ± 2	43 ± 3	44 ± 6	42 ± 6	40 ± 1	43 ± 4
$rCMRO_2$ ($ml \cdot min^{-1} \cdot 100\ ml^{-1}$)									
before	4.83 ± 0.81	5.22 ± 0.70	4.36 ± 0.79	3.94 ± 0.70[b]	3.49 ± 0.50[b]	4.52 ± 0.90[b]	3.49 ± 0.43[b]	1.41 ± 0.29	3.86 ± 0.60[b]
after	4.68 ± 0.72	5.35 ± 0.69	4.86 ± 0.81	4.23 ± 0.76	3.48 ± 0.60[b]	4.77 ± 0.80[b]	3.54 ± 0.79[b]	1.68 ± 1.02	4.01 ± 0.77[b]
normal	5.52 ± 0.82	5.75 ± 0.82	5.10 ± 0.68	4.90 ± 0.72	4.77 ± 0.67	5.99 ± 0.57	4.46 ± 0.71	1.54 ± 0.27	5.03 ± 0.68

[a] rCBF, regional cerebral blood flow; rCBV, regional cerebral blood volume; rOER, regional oxygen extraction ratio; $rCMRO_2$, regional cerebral metabolic rate of oxygen; rhEPO, recombinant human erythropoietin.
[b] $P < 0.05$, compared with healthy control subjects.
[c] $P < 0.01$, compared with pretreatment values.
[d] $P < 0.001$, compared with pretreatment values.
[e] $P < 0.05$, compared with pretreatment values.
[f] $P < 0.01$, compared with healthy control subjects.
[g] $P < 0.001$, compared with healthy control subjects.

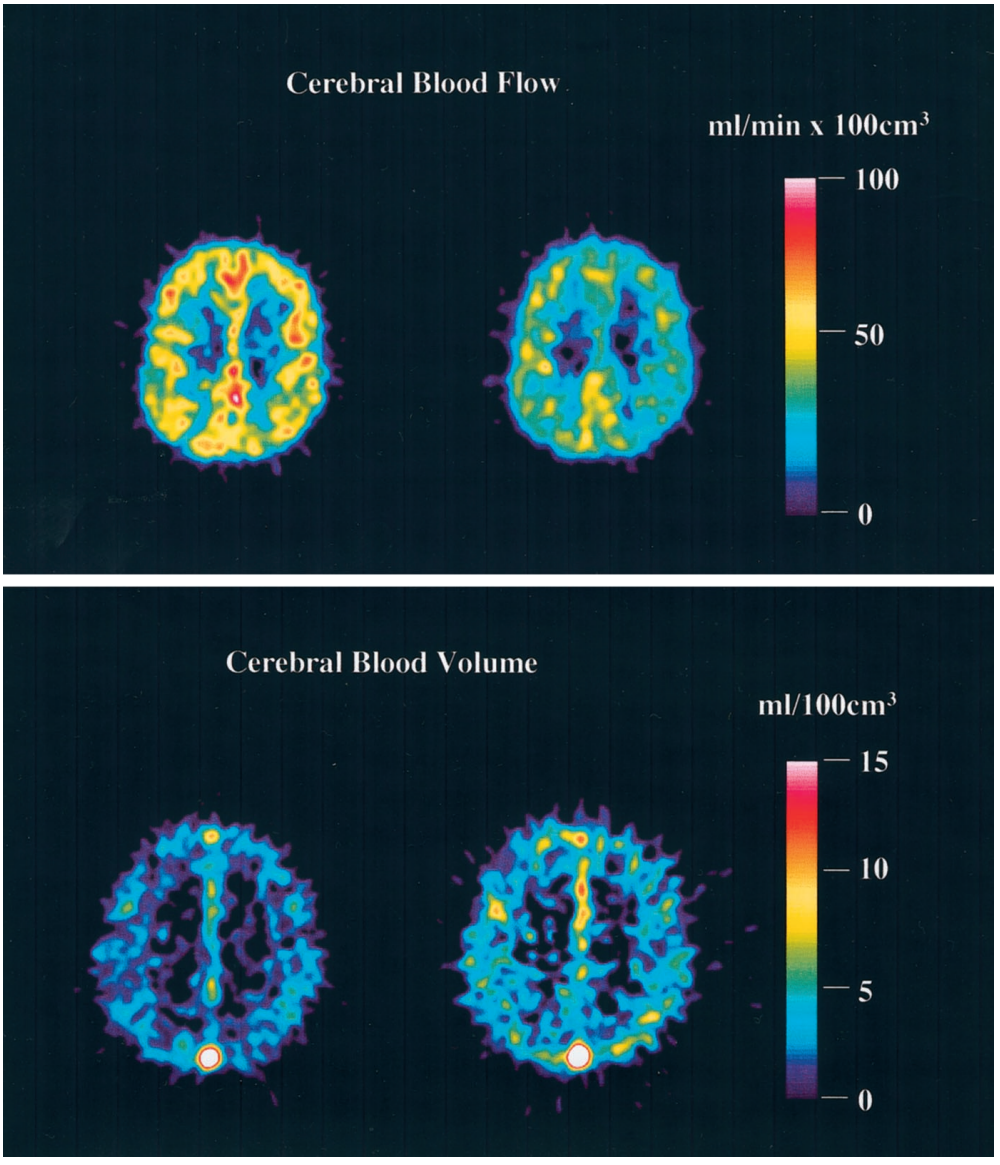

Figure 1. Hemispherical regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) in hemodialysis patients in the anemic stage (left) and after normalization of hematocrit (right). In Panel a, the rCBF decreased, whereas Panel b the rCBV increased after normalization of hematocrit, as guided by the color scale.

In healthy humans, within the autoregulatory range (MAP between 60 and 160 mmHg), as CPP falls there is, within seconds, vasodilation and an increase in rCBV to keep rCBF constant (28). When the vasodilation has almost reached its maximum and rCBV can no longer increase, and if CPP continues to fall due to a fall in MAP, rCBF starts to decline; in other words, the cerebral perfusion reserve becomes exhausted and the metabolic activity is maintained by increasing rOER (28). It was considered that rCBF/rCBV is a measure of cerebral hemodynamic perfusion reserve. When the ratio is below about 6, vasodilation and rCBV are maximal and the reserve is exhausted, even if rCBF is still normal (29).

In the present study, normalization of the Hb value was accompanied by an increase rCBV, reflecting in the occurrence of cerebral vasodilation. The rCBF/rCBV ratio, representing the cerebral hemodynamic perfusion reserve, decreased with normalization of Hb but without reaching the critical value, *i.e.*, 6, which could not explain the increase in rOER. Schäbitz (30) found that an increased blood and plasma viscosity, a decreased deformability of erythrocytes, and increased tendency to aggregation are pathogenetically important for a disturbance of the microcirculation. Of special importance among these factors is the decreased erythrocyte deformability, when the erythrocytes have difficulty in traversing the capillaries resulting in a low perfusion rate in these capillaries, which will make the transfer of oxygen more difficult (31). Therefore, we assume that normalization of the hematocrit in our group of patients with hemorheologic abnormalities, *i.e.*, decreased erythrocyte fluidity and high plasma viscosity, would have lowered the velocity of erythrocyte transfer inside the brain capillaries and may explain the high oxygen extraction by the brain tissue. In addition, rigidity of the vascular wall due to

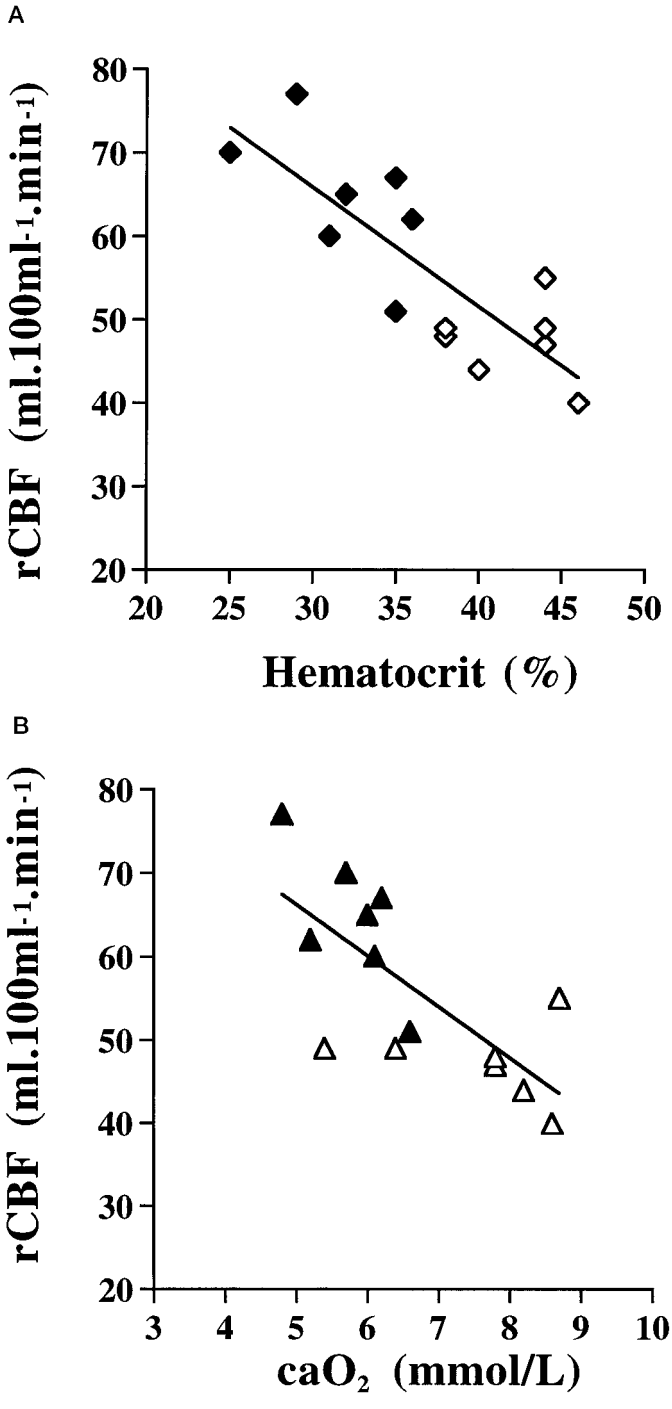

Figure 2. Hemispherical regional cerebral blood flow is significantly correlated with the hematocrit (A) ($r = 0.87$, $P < 0.001$) and with a lesser degree of significance to arterial oxygen content (B) (caO_2) ($r = 0.68$, $P < 0.05$). Filled symbols, before erythropoietin (EPO) treatment; open symbols, after EPO treatment.

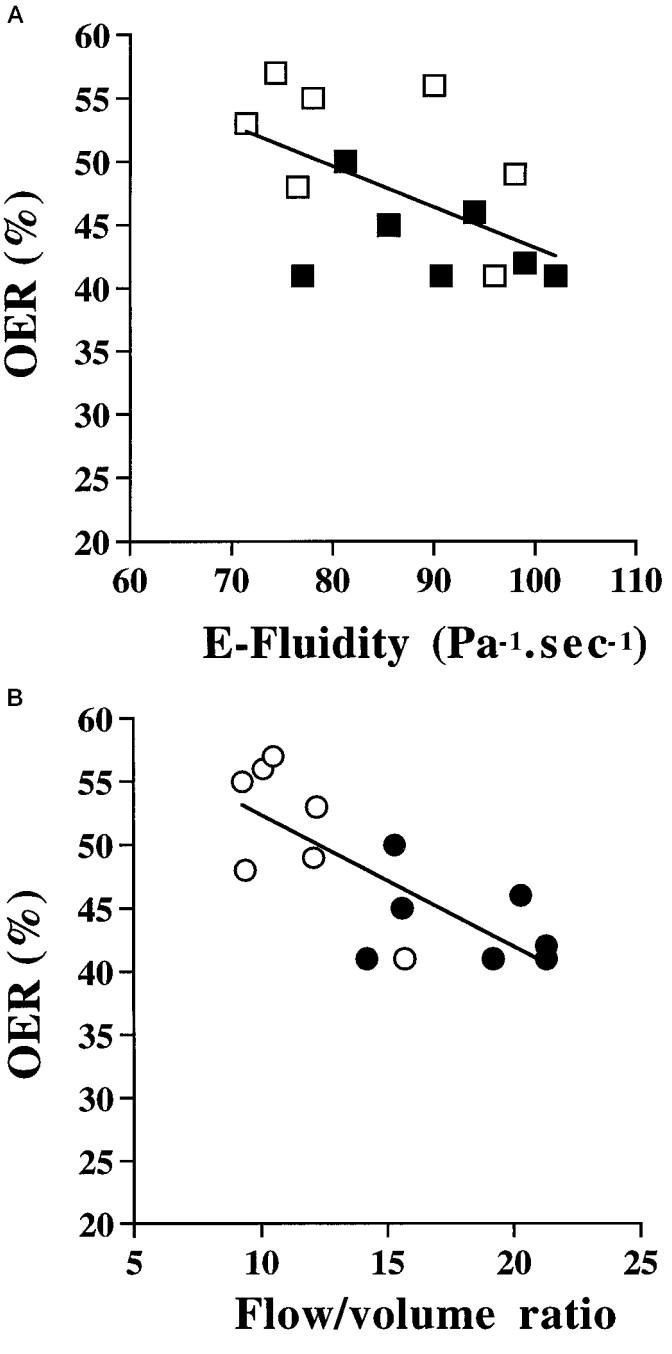

Figure 3. Hemispherical oxygen extraction ratio (rOER) was significantly correlated with the erythrocyte fluidity (A) ($r = 0.6$, $P < 0.05$), and with the ratio of regional cerebral blood flow to regional cerebral blood volume (rCBF/rCBV) (B) ($r = 0.72$, $P < 0.05$), which represents the cerebral hemodynamic perfusion reserve. Filled symbols, before erythropoietin (EPO) treatment; open symbols, after EPO treatment.

atherosclerosis, a common finding in uremic patients (32), would make the viscosity of the blood essentially the main determinant of blood flow in accord with Poiseuille's law.

Another important factor is that most of the patients in our study had hypercholesterolemia, which increases the risk of atherosclerosis, and hyperfibrinogenemia, which negatively affects the whole blood and plasma viscosity as well as the deformability and aggregability of red blood cells, causing a reduction in the microcirculatory flow (33). Thus, reduction of plasma fibrinogen and blood cholesterol may help to improve the microcirculatory blood flow and allow the patients to gain benefit from raising the hemoglobin value.

In summary, Eschbach *et al.* (7) demonstrated an improvement in the quality of life when Hct was raised to 42%. Bárány *et al.* (34) reported that the exercise capacity increased with normalization of Hct, but still remained subnormal compared with EPO-treated nonuremic subjects. From another study (35), it has been suggested that raising Hct to 42% from the commonly achieved target of 30% significantly improves the brain cognitive function. In our study, normalization of Hct greatly improved the general condition of the HD patients, but on the other hand the fraction of oxygen extraction by the brain tissue increased. The reason for this is not clear, but we assume that it may be attributed to a decrease in erythrocyte velocity inside the brain capillaries due to the coexisting problems of decreased erythrocyte fluidity and increased plasma viscosity in the these patients. In our view, an adequate hemoglobin concentration that fulfills the oxygen demand is an individual characteristic of every patient. Although Hino *et al.* (36) reported that a normal hematocrit provides a better brain oxygenation than any level lower than normal, their study was conducted on normal subjects with healthy erythrocytes, but the condition needs to be evaluated in patients with poorly deformable erythrocytes. However, our study comprised only a small number of patients, and more confirmative studies with a larger number of patients need to be undertaken.

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