

Extracorporeal Double Filtration Plasmapheresis in Acute Atherothrombotic Brain Infarction Caused by Major Artery Occlusive Lesion

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Extracorporeal double filtration plasmapheresis (EDFP) can quickly lower plasma viscosity and fibrinogen concentration. EDFP has the potential to improve cerebral microcirculation in acute ischemic stroke and ultimately to salvage penumbral tissue. However, no evidence is available to show that EDFP can increase cerebral blood flow (CBF). Therefore, we investigated whether EDFP could increase CBF by quantitative CBF measurements and documented the clinical effects of EDFP in acute ischemic stroke. EDFP was performed ten times in seven patients diagnosed as having acute atherothrombotic brain infarction caused by major artery occlusive lesion. They also fulfilled one of the following entry criteria: 1) diffusion/perfusion mismatch demonstrated by MRI on admission; 2) a hemispheric syndrome, but only a small lesion on diffusion weighted MRI (< 25% of MCA territory); or 3) progressing stroke. Exclusion criteria were 1) contraindication of heparin or 2) spontaneous improvement of symptoms. Time from stroke onset to EDFP varied from 5 hr to 7 days. Plasma viscosity was quickly lowered by EDFP without affecting RBC counts, Hb, or Hct in all patients. Positron emission tomography (PET) with 15-O labeled H₂O measurements revealed a significant CBF increase from 36.4 ± 8.3 ml/100 g/min to 40.7 ± 6.8 ml/100 g/min in the affected hemisphere (P = 0.048). Definite CBF improvement was also demonstrated by single photon emission computed tomography (SPECT) in one of two patients who had severe stenosis of the middle cerebral artery. Furthermore, this patient showed remarkable improvement of hemiplegia immediately following EDFP (NIHSS score: 18 to 13). In conclusion, EDFP can increase CBF in ischemic brain tissue in acute atherothrombotic brain infarction. Further clinical studies should focus on the efficacy of EDFP on outcome of patients with this stroke subtype. *J. Clin. Apheresis* 18:167–174, 2003. © 2003 Wiley-Liss, Inc.

Key words: plasmapheresis; brain ischemia; cerebral blood flow; recanalization

INTRODUCTION

The ischemic penumbra is a major target in the treatment of acute brain infarction. A reversal of ischemic neurological deficits can be achieved by blood flow restoration in the penumbral tissue. In fact, striking improvements of ischemic neurological deficits have been documented after the early reopening of occluded vessel by spontaneous clot lysis [1–3] or thrombolytic therapy [4–6]. Recent progress in magnetic resonance imaging has enabled us to identify a diffusion/perfusion mismatch area as the ischemic area with a high risk of progression to irreversible damage [7,8]. If local perfusion does not improve within a certain time frame, a significant part of the penumbra or the mismatch area will deteriorate to infarct [9]. Injection of recombinant tissue-type plasminogen activator (rt-PA) can significantly improve outcome if it is initiated within 3 hr of stroke

onset [4]. However, fewer than 5% of stroke patients receive rt-PA therapy because of this time constraint and other limiting criteria [10]. Even when the occluded vessel can not be opened, the blood flow restoration in penumbral tissue could theoretically be

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achieved by a rheological modification. Based on the Hagen-Poiseuille equation ($Q = \Delta P r^4 / 8 L \eta$ where Q is blood flow, ΔP is the pressure gradient, r is the vessel radius, L is length, and η is the viscosity), blood flow can be increased by lowering the blood viscosity [11]. Effects of hematocrit (Hct) lowering by venesection and infusion on acute stroke have been investigated by several randomized trials [12–16]. However, no clinical studies have succeeded in confirming any favorable effects of these hemodilution therapies. Recently, extracorporeal plasmapheresis was applied to ischemic stroke patients to quickly lower their plasma viscosity by the removal of macromolecules from plasma without removal of red blood cells (RBC), so as not to reduce oxygen transport capacity [17–20]. This process also lowers the fibrinogen concentration. It is known that a high level of fibrinogen concentration is an independent risk factor for development of stroke. Thus extracorporeal plasmapheresis would appear to be an ideal method for rheological intervention in the acute stage of ischemic stroke. However randomized study failed to demonstrate any beneficial effects of extracorporeal double filtration plasmapheresis (EDFP) in patients with sudden onset of ischemic hemispheric stroke within 6 hr [18]. We suspect that this failure might be the result of patient selection. Because sudden onset in seconds or minutes of a maximum neurological deficit is one of the characteristic features of embolic stroke, patients with embolic occlusion of a major cerebral artery would have been included in the previous study. In embolic infarction, there is usually not time for collateral circulation to become established, and the cerebral blood flow (CBF) decline is usually greater than in atherothrombotic infarction. Therefore, the beneficial effects of rheological modification by EDPF would be better demonstrated in patients with atherothrombotic brain infarction caused by major artery occlusive lesion that shows a diffusion/perfusion mismatch or in patients with a progressing stroke. In such patients, a large amount of hemodynamically compromised tissue including ischemic penumbra would be present. We undertook an investigation of such patients to determine if EDPF increased CBF in ischemic brain tissue and whether any reversal of ischemic neurologic deficits could be observed after EDPF.

MATERIAL AND METHODS

We studied seven patients with a mean age of 65.4 ± 6.6 years, who were admitted to our Stroke Care Unit from September 1999 to December 2000. They were diagnosed as having an acute atherothrombotic brain infarction caused by occlusive dis-

ease of a major cerebral artery, which was confirmed by cerebral angiography or magnetic resonance angiography (MRA) on admission. They also fulfilled one of the following entry criteria: 1) diffusion/perfusion mismatch demonstrated by MRI on admission; 2) a hemispheric syndrome, but only a small lesion on diffusion weighted MRI (<25% of MCA territory); or 3) progressing stroke. A hemispheric syndrome was defined as a complex of neurological deficits that consisted of various degrees of hemiparesis, consciousness disturbance, conjugate ocular deviation, and cortical signs such as aphasia or neglect syndrome. Patients were excluded if they had 1) cardioembolic stroke, 2) contraindication of heparin, or 3) spontaneous improvement of symptoms. The vascular lesions and clinical picture of the seven patients are listed in Table I. Diffusion/perfusion mismatch was observed in three patients (patients 1, 3, and 4 in Table I). A 1.5 T EPI-equipped whole body scanner was used (MAGNETOM VISION, Siemens Medical Systems, Inc., South Iselin, NJ) and isotropic diffusion-weighted images were obtained by using a multislice, single-shot spin-echo EPI sequence (b value = 1,000). Perfusion-weighted images were obtained after a bolus of gadolinium-DTPA and time-to-peak images were created. Three patients were enrolled because of a hemispheric syndrome with only a small infarct volume on the initial diffusion weighted MRI (patients 2, 6, and 7 in Table I). The other patient was also enrolled because of a gradual progression of ischemic symptoms resulting from basilar artery occlusion (patient 5).

After obtaining a written informed consent from the next of kin of each patient, EDPF was started. A double lumen catheter (Flexicon dual lumen DLC-4010, Vas-cath Inc., Ontario, Canada) was inserted into the femoral vein. For the primary plasma separation and the plasma differential separation, a Plasmaflo OP-05W and a Cascadeflo AC-1760 (Asahi Medical Co., Tokyo) were used, respectively. Heparin was continuously injected at 2,500 IU/hr. The procedure lasted about 90 min and 1.0–2.0L of plasma were filtered. Blood sampling was performed before and after EDPF to measure blood viscosity and other various rheological and biochemical parameters including LDL-cholesterol, fibrinogen, and α 2-macroglobulin. It is known that plasma viscosity can be quickly lowered after EDPF but will gradually return to the initial hemorheological condition. To maintain low plasma viscosity level, EDPF should be repeated every 12 to 24 hr [18]. We repeated EDPF when fluctuation of symptoms and signs was observed more than 24 hr after the initial EDPF.

Quantitative CBF measurements were performed by using positron emission tomography (PET) (ECAT EXACT47, Siemens Medical Systems, Inc.) with the

TABLE I. Patient Profiles and Changes in Plasma Viscosity, Fibrinogen Concentration, and Neurological Deficits Before and Immediately After Initial Extracorporeal Double Filtration Plasmapheresis (EDFP)*

Patients	Vascular lesion	EDFP	Timing	Plasma viscosity (mPa)	Fibrinogen (mg/dl)	NIHSS score
						before and after EDFP ^a
1.54, M	Lt. IC occlusion	1st	14 h	1.503 → 1.289	423 → 248	12 → 12 (4)
2.62, M	Rt. M1 occlusion	1st	4 days	1.673 → 1.493	385 → 278	13 → 13 (5)
3.62, M	Lt. M1 stenosis	1st	8 h	1.369 → 1.188	243 → 138	18 → 13 (6)
4.74, M	Rt IC stenosis	1st	7 days	1.576 → 1.436	439 → 254	5 → 5 (3)
5.70 M	BA stenosis	1st	4 days	1.464 → 1.287	297 → 221	19 → 19 (16)
6.69, M	Rt. IC stenosis	1st	11 h	1.394 → 1.197	234 → 164	17 → 17 (13)
7.67, M	Rt. IC stenosis	1st	15 h	1.288 → 1.184	255 → 191	17 → 17 (0)
Mean ± SD			2.4 ± 2.6 day	1.467 ± 0.131 → 1.296 ± 0.124	325.1 ± 88.4 → 213.4 ± 51.2	14.4 ± 4.9 → 13.7 ± 4.6
P value				P < 0.0001	P = 0.001	n.s.

*IC, internal carotid artery; M1, stem of the middle cerebral artery; BA, Basilar artery; NIHSS, NIH Stroke Scale.

^a) NIHSS score at one month after onset.

TABLE II. Cerebral Blood Flow (CBF) Change Before and Immediately After Extracorporeal Double Filtration Plasmapheresis (EDFP)*

Patients	Vascular lesion	EDFP	Timing	Plasma viscosity (mPa)	Fibrinogen (mg/dl)	CBF change (ml/100 g/min)	
						Affected hemisphere	Non-affected hemisphere
1.54, M	Lt. IC occlusion	2nd	6 days	1.514 → 1.391	321 → 248	Lt: 37.9 → 45.8	Rt: 52.3 → 52.4
2.62, M	Rt. M1 occlusion	1st	4 days	1.673 → 1.493	385 → 278	Rt: 28.7 → 32.6	Lt: 45.3 → 44.9
3.62, M	Lt. M1 stenosis	1st	8 h	1.369 → 1.188	243 → 138	(SPECT: significant improvement)	
4.74, M	Rt. IC stenosis	1st	7 days	1.576 → 1.436	439 → 254	Rt: 47.9 → 48.9	Lt: 42.0 → 41.5
5.70 M	BA, Lt M1 stenosis	2nd	9 days	1.479 → 1.370	291 → 220	Lt: 28.9 → 35.4	Rt: 27.9 → 35.7
6.69, M	Rt IC stenosis	2nd	7 days	1.607 → 1.281	371 → 236	Rt: 39.4 → 40.4	Lt: 34.3 → 34.3
7.67, M	Rt. IC stenosis	1st	15 h	1.288 → 1.184	255 → 191	(SPECT: no significant change)	
Mean ± SD		4.9 ± 3.3 day		1.501 ± 0.135 → 1.335 ± 0.120	329.3 ± 72.3 → 223.6 ± 46.6	36.4 ± 8.3 → 40.7 ± 6.8	40.6 ± 9.2 → 41.7 ± 7.4
P value				P = 0.0013	P = 0.0006	P = 0.048	n.s.

*IC, internal carotid artery; M1, stem of the middle cerebral artery; BA, Basilar artery; NIHSS, NIH Stroke Scale.

¹⁵O-labeled water bolus injection method before and after the first or second EDFP in five patients. The spatial resolution of the PET scanner was 4.5 mm in-plane at full width at half maximum and 4.5 mm axially. Patients were positioned on the PET couch in the supine position and the right brachial artery was catheterized for obtaining the blood counts and monitoring the blood pressure. The head was firmly fixed in a headrest restraint with a plastic collar (Philadelphia Collar, Canada). During the acquisition of PET scans, arterial blood pressure and ECG were continuously monitored. Using a power injection system (CYPRIS®, ¹⁵O-water injection module, O1-C, Sumitomo Heavy Industries, Ltd.), a 943.5 MBq of H₂¹⁵O was injected via a 22-gauge Teflon cannula inserted into the left antecubital vein through a 0.22 µm filter (MILLEX-GV, Millipore Co., Ltd., Billerica, MA) at a rate of 0.4 ml/sec for 50 sec with saline flushing. Arterial blood was continuously withdrawn at a constant speed of 3.82 ml/min using an infusion/withdrawal pump (Harvard Apparatus, South Natic, MA). The radioactivity concentration in the ar-

terial blood was measured using a beta-ray detector (Hamamatsu Photonix, Japan) to calculate the input function. Blood withdrawal was started 10 sec prior to the ¹⁵O-labeled water injection and continued until 180 sec after the injection. The acquisition time for each CBF measurement was 90 sec. Mean CBF values were calculated by placing circular regions of interest (ROIs) in the cortical area. Because of the constancy of arterial PaCO₂ levels before and after the EDFP, CBF values were not corrected by CO₂ levels. In the other two patients, PET measurement was not performed but qualitative CBF evaluations were performed using single photon emission computed tomography with ^{99m}Tc-hexa-methylpropylene amineoxime (^{99m}Tc-HMPAO-SPECT) before and after the initial EDFP.

RESULTS

EDFP was performed 10 times in seven patients. The initial EDFP was started from 5 hr to 4 days after the onset of ischemic symptoms. EDFP significantly

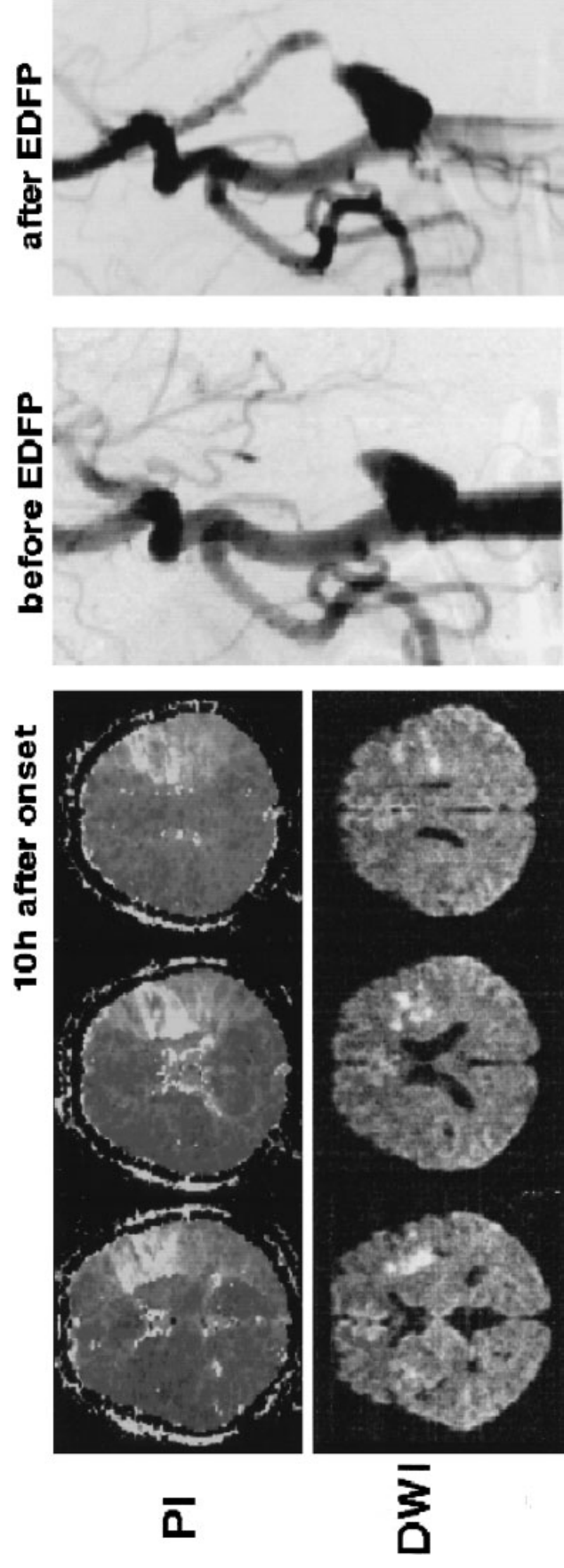


Fig. 1. MRI images and cerebral angiograms in Patient 1. PI, perfusion image (time-to-peak image); DWI, diffusion-weighted image.

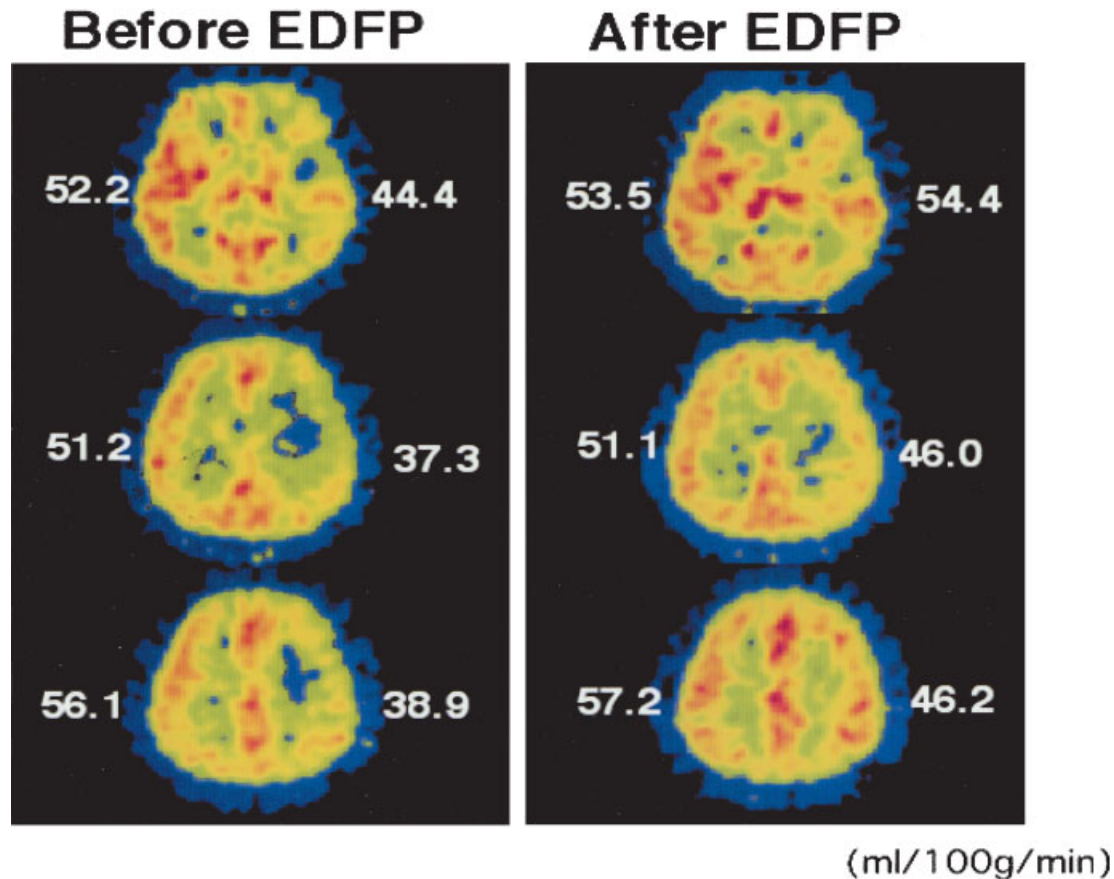


Fig. 2. PET images just before and after the plasmapheresis in Patient 1. A CBF increase of up to 10 ml/100 g/min was observed in the left hemisphere ipsilateral to the occlusion. No significant change was observed in CBF in the contralateral hemisphere.

lowered LDL-cholesterol, fibrinogen, and α 2-macroglobulin (354.3 ± 134.8 to 209.3 ± 72.4 mg/dl, 325.1 ± 88.4 to 213.4 ± 51.2 mg/dl, and 152.4 ± 73.3 to 107.0 ± 48.3 mg/dl, respectively). Plasma viscosity also significantly decreased from 1.467 ± 0.131 to 1.296 ± 0.124 mPas ($P < 0.0001$) but there was no significant change in NIH Stroke Scale score before and just after the initial EDFP (Table I). There were no significant changes in whole blood viscosity, RBC counts, hemoglobin, Hct, serum electrolyte concentrations, prothrombin time, active prothrombin time, plasminogen, anti-thrombin III level, or D-dimer (data not shown). PET measurements revealed a CBF increase up to 10 ml/100 g/min in the ischemic hemisphere (36.4 ± 8.3 to 40.7 ± 6.8 ml/100g/min, $P = 0.048$). However, no significant increase was observed in the non-affected hemisphere (Table II). Definite CBF improvement after EDFP was also demonstrated on SPECT images in one of the other two patients who had severe stenosis of the MCA (patient 3 in Table II). This patient's hemiplegia showed definite improvement immediately after EDFP (NIH stroke scale score: 18 to 13). Repeated vascular examination revealed recanalization of the occluded internal carotid artery in one patient

(patient 1 at 10 days after EDFP) and improvement of perfusion abnormality in MRA in one patient (patient 3 at 20 hr after EDFP).

Illustrative Cases

Patient 1. A 54-year-old man, with a 5-year history of treated hypertension, was admitted for the right hemiparesis and aphasia. Blood pressure was 196/116 mmHg and routine blood tests were normal. NIH stroke scale score was 12. Cerebral angiography revealed an occlusion of the left internal carotid artery (ICA), and diffusion/perfusion mismatch was demonstrated in the ipsilateral hemisphere 10 hr after the onset of ischemic symptoms (Fig. 1). Transesophageal echocardiography and transoral carotid ultrasound did not reveal any specific embolic source nor the findings of carotid dissection [21,22]. We diagnosed the occlusion was atherothrombotic in nature. EDFP was initiated 14 hr after onset. Plasma viscosity and fibrinogen concentration were decreased from 1.503 to 1.289 mPa and from 423 to 248 mg/dl, respectively. Aphasia was slightly improved but NIH stroke scale score was not changed after EDFP. The second EDFP was performed 6

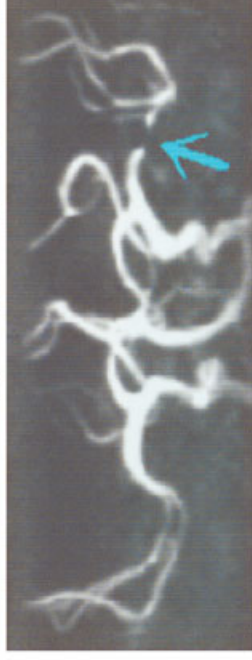
A. Before EDFFP

B. 20h after EDFFP

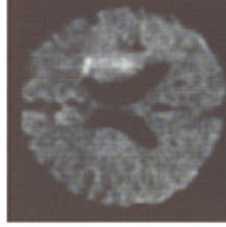
MR angiography



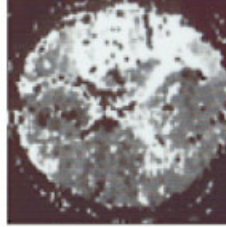
MR angiography



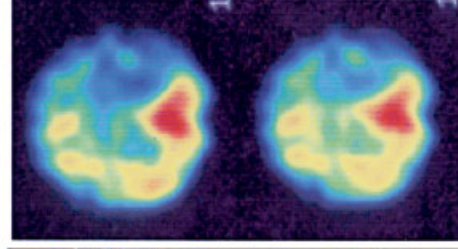
DWI



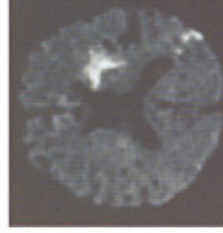
PI



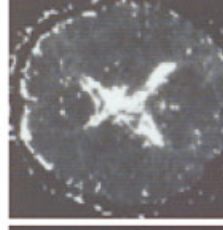
PAO-SPECT



DWI



PI



PAO-SPECT

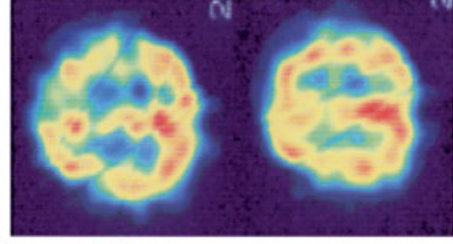


Fig. 3. Neuroradiological assessment before and after the plasmapheresis in Patient 3. **A:** Before the extracorporeal double filtration plasmapheresis (EDFFP), MR angiography revealed severe stenosis in the middle cerebral artery (arrow) and diffusion/perfusion mismatch was observed in diffusion-weighted image (DWI), perfusion image (PI), and ^{99m}Tc -HMPAO-SPECT. **B:** Twenty hr after the EDFFP, improvement of distal opacification of the middle cerebral artery was demonstrated by MR angiography (arrow). A significant CBF improvement was observed both in ^{99m}Tc -HMPAO-SPECT and perfusion image (PI), and consequently a diffusion/perfusion mismatch was not observed.

days after onset with the monitoring of CBF by quantitative PET imaging. After the second EDFP, plasma viscosity and fibrinogen concentration were decreased from 1.514 to 1.391 mPa and from 321 to 248 mg/dl, respectively. The baseline CBF study showed an area of significant hypoperfusion over the left MCA territory. A significant increase of CBF was observed after EDFP in the ischemic hemisphere from 37.3 to 46.0 ml/100 g/min (Fig. 2). Ten days after the onset of stroke, a duplex ultrasonographic examination detected recanalization of the occluded left ICA. This was confirmed by cerebral angiography performed before the carotid endarterectomy, which was performed 1.5 months after the onset (Fig. 1). After the carotid endarterectomy, the patient was discharged with an NIH stroke scale score of 4 and Rankin scale of 1.

Patient 3. A 62-year-old man, with a 3-year history of treated diabetes and hypertension, presented with right hemiplegia, conjugate ocular deviation to the left, and global aphasia. On admission, CT scan showed only a slight cerebral atrophy. Blood pressure was 140/80 mmHg and routine blood tests were normal. NIH stroke scale score was 18. Four hr after the onset of symptoms, MRA and MRI studies revealed a severe stenosis of the left MCA trunk and diffusion/perfusion mismatch in the left hemisphere; ^{99m}Tc -HMPAO-SPECT also demonstrated severe hypoperfusion over the left MCA territory. EDFP was started 8 hr after onset. Plasma viscosity and fibrinogen concentration were decreased from 1.369 to 1.188 mPa and from 243 to 138 mg/dl, respectively. During EDFP, his neurological deficits gradually improved. At the end of the EDFP, he could raise his right arm and leg. NIH stroke scale score improved from 18 to 13. Twenty hr after the EDFP, MRI studies and ^{99m}Tc -HMPAO-SPECT were repeated. An improvement of the stenotic lesion of the left MCA was revealed by MRA. The ischemic lesion on the diffusion MRI was not enlarged and the diffusion/perfusion mismatch had vanished. The ^{99m}Tc -HMPAO-SPECT also demonstrated a dramatic CBF improvement in the MCA territory (Fig. 3). He was discharged with an NIH stroke scale score of 6 and Rankin scale of 1.

DISCUSSION

The therapeutic principle of EDFP in acute ischemic stroke is to increase CBF in penumbral tissues by reducing plasma viscosity and ultimately to minimize ischemic neurological deficits. However, little work has been done to study whether EDFP can increase CBF in acute stroke patients. As far as we know, the present study is the first designed to elucidate the quantitative

change in CBF after EDFP in acute ischemic stroke. Quantitative CBF can be repeatedly measured by PET with H_2^{15}O within 2 min. It is ideal to monitor CBF change by PET during all EDFP procedures. However, PET measurement was performed in five of ten EDFP because of the technical complexity. The observed maximum CBF increase in our study was 10 ml/100 g/min. Previous human PET studies have demonstrated that a region with CBF between 12 and 22 ml/100 g/min can be characterized as an ischemic penumbra [23,24]. Thus the extent of the CBF increase we have demonstrated is sufficient to salvage the penumbral tissue. It is of great interest that the CBF increase was observed only in the ischemic hemisphere ipsilateral to the major cerebral artery that had the occlusive lesion. This observation concurs with the results of an experimental study using rats. Lenz et al. [25] demonstrated that changes in blood viscosity do not result in changes in the CBF as long as the blood vessels retain their capacity to compensate for the changes in viscosity by vasodilating with increased viscosity and vasoconstricting with decreased viscosity. It is well known that, even in the normal brain, a significant increase in CBF can be induced by lowering the hematocrit. A recent experimental study demonstrated that 40–60% of the increased CBF after venesection and infusion could be the result of compensatory vasodilation due to reduction of arterial oxygen content. This would imply that hematocrit lowering, although widely accepted as a method of hemodilution, cannot achieve a penumbra rescue [26].

In a clinical setting, EDFP should be used in patients who have an ischemic penumbra and who will thus benefit from EDFP and show definite recovery from ischemic neurological deficits. Therefore we only selected patients with lesions on DWI smaller than the ischemic area that would be suspected, based on neurological signs or perfusion images, or patients with progressing stroke caused by atherothrombotic major cerebral artery occlusion. We succeeded here in demonstrating a favorable recovery in four patients. In these patients, the NIH Stroke Scale score improved more than 8 points from baseline (5–17 points) in the first month after EDFP (Table I). A definite reversal of neurological deficits was demonstrated immediately following EDFP in patient 3. In this patient, we observed dramatic improvement of MRA finding as well as CBF improvement. Recanalization of an occluded vessel was observed in one patient 10 days after EDFP. This might be merely the natural course. On the other hand, we could hypothesize that significant reduction of fibrinogen concentration achieved with EDFP accelerate the recanalization of occluded vessels by the lysis of fresh thrombi that were superimposed on an atherosclerotic arterial lesion. It has been shown that the reduction of fibrinogen concentration may be ben-

eficial in ischemic stroke. In one study, a significant improvement of functional status at 90 days after stroke onset was demonstrated in patients with intravenous ancrod, a purified fraction of venom from the Malaysian pit viper (*Calloselasma rhodostoma*) to achieve rapid defibrinogenation [27]. In addition, increased cerebral CO₂ reactivity after defibrinogenation by ancrod or heparin-mediated extracorporeal LDL precipitation (HELP) has also been demonstrated in humans [28,29].

In conclusion, EDFP has the potential to improve CBF in ischemic tissues and to ultimately salvage penumbral tissues. Given the positive findings of this study, further prospective studies are required, especially in patients with atherothrombotic infarction.

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