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Quantitative Measurement of Oxygen Extraction Fraction by MRI in Patients with Cerebrovascular Disease: Pre- and Post-Surgery

Serebrovasküler Hastalıklı Hastalarda Oksijen Ekstraksiyon Fraksiyonunun MRG ile Kantitatif Ölçümü: Cerrahi Öncesi ve Sonrası

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ABSTRACT

AIM: We aimed to evaluate cerebral hemodynamic status of preoperative and postoperative revascularization treatment by oxygen extraction fraction (OEF)-magnetic resonance imaging (MRI) in patients with severe cerebrovascular stenosis or occlusive disease.

MATERIAL and METHODS: This study enrolled 9 symptomatic patients with severe cerebrovascular disease and 9 age-matched normal volunteers. Cerebral blood flow (CBF) and OEF were determined in all subjects by functional MRI. Brain regions with elevated OEF above normal range were defined in the patients preoperatively. The values of pre- and postoperative OEF in these regions were compared.

RESULTS: A total of 16 regions of interest (ROIs) had elevated OEF before the vascular surgery, with relative CBF (rCBF) values ranging from 0.2 to 1.0. OEF decreased to normal range in 15 ROIs postoperatively, which indicated hemodynamic improvement in these regions. The OEF value of the high-OEF group (preoperative OEF value ranged from 0.365 to 0.400) had a significant decrease compared with those of the low-OEF group (preoperative OEF value ranged from 0.350 to 0.365), which showed an a statistical difference ($p = 0.001$).

CONCLUSION: OEF was elevated in patients with severe ischemic cerebrovascular disease, and decreased after successful revascularization. OEF-MRI can provide quantitative information for evaluating the hemodynamic status and selecting the candidates suitable for revascularization.

KEYWORDS: Oxygen extraction fraction (OEF), Cerebral blood flow (CBF), Magnetic resonance imaging (MRI), Stent, Superficial temporal artery-middle cerebral artery (STA-MCA), Bypass

ÖZ

AMAÇ: Şiddetli serebrovasküler stenoz veya oklüzif hastalığı olan hastalarda oksijen ekstraksiyon fraksiyonu (OEF) - manyetik rezonans görüntüleme (MRG) ile preoperatif ve postoperatif revaskülarizasyon tedavisiyle serebral hemodinamik durumunu değerlendirmeyi amaçladık.

YÖNTEM ve GEREÇLER: Çalışmaya şiddetli serebrovasküler hastalıklı 9 semptomatik hasta ve yaş bakımından eşleşmiş 9 normal gönüllü katıldı. Serebral kan akışı (CBF) ve OEF tüm deneklerde fonksiyonel MRG ile belirlendi. Hastalarda preoperatif olarak OEF seviyesi normal aralığın üzerine yükselmiş beyin bölgeleri belirlendi. Bu bölgelerde preoperatif ve postoperatif OEF karşılaştırıldı.

BULGULAR: Vasküler cerrahiden önce 16 ilgilenilen bölgede (ROI) artmış OEF vardı ve relatif CBF (rCBF) değerleri 0,2 ile 1,0 arasında değişmekteydi. OEF postoperatif olarak 15 ROI'de normal aralığa indi ve bu durum bu bölgelerde hemodinamik iyileşmeye işaret etmekteydi. Düşük OEF grubundaki (preoperatif değer 0,350 ile 0,365 arasında) OEF değerinde yüksek OEF grubuna göre (preoperatif OEF değeri 0,365 ile 0,400 arasında) önemli ölçüde bir azalma vardı ($p = 0,001$).

SONUÇ: Şiddetli iskemik serebrovasküler hastalığı olan hastalarda OEF artmıştı ve başarılı revaskülarizasyon sonrasında azaldı. OEF-MRG, hemodinamik durumu değerlendirmek ve revaskülarizasyon için uygun adayları seçmek açısından kantitatif bilgiler sağlayabilir.

ANAHTAR SÖZCÜKLER: Oksijen ekstraksiyon fraksiyonu (OEF), Serebral kan akışı (CBF), Manyetik rezonans görüntüleme (MRG), Stent, Süperfisial temporal arter-orta serebral arter (STA-OSA), Bypass

INTRODUCTION

Cerebral misery perfusion is an important differential diagnosis in post-stroke patients presenting with collapse in the presence of hemodynamically significant cerebrovascular stenosis (7). Some studies have indicated that patients with misery perfusion in stage II ischemia carry higher risk of stroke recurrence than those without misery perfusion after medical therapy (11, 17), and these patients should accept surgical intervention for better recovery (3, 15, 22). However, whether patients with severe cerebrovascular stenosis or occlusion disease receive additional benefits from revascularization after medical treatment on prevention of predictable stroke is still under debate. Therefore, it is important to evaluate the hemodynamic status changes of those patients with cerebrovascular disease (8).

Oxygen extraction fraction (OEF) has been recognized as an accurate predictor of misery perfusion that represents the decompensated stage of brain tissue energy budget of the patients with chronic ischemic diseases (11, 15, 17, 20). Positron emission tomography (PET) is the most reliable method to measure these hemodynamic changes (8). However, high cost and limited facilities restrict PET for being used to characterize hemodynamic status.

A new technique, magnetic resonance imaging (MRI) has been used to indicate cerebral hemodynamics in recent years. MRI analyzes the variation in susceptibility and provides information of brain perfusion pattern (6). MRI can also measure the reaction of cerebral hemodynamics in hypercapnia and cerebrovascular reserve, which can be assessed using blood oxygenation level dependent (BOLD) functional MRI. In the previous study, quantitative measurement of OEF was realized by using BOLD imaging (2). The BOLD imaging technique has been tested in volunteers and present a decreasing effect of OEF assessment in hypercapnia patients (1). In our previous study, we used this promising technique to detect misery perfusion, which is characterized by elevated oxygenation in ischemic region (23).

In this study, we aimed to investigate the cerebral hemodynamic abnormalities and follow-up the hemodynamic change after revascularization by using OEF-MRI in patients undergoing cerebrovascular surgical treatment.

MATERIAL and METHODS

Subjects

Nine patients undergoing unilateral cerebrovascular surgical treatment and nine age-matched normal subjects were enrolled in this study. The inclusion criteria for patients were as follow:1) older than 40 years old; 2) presented with symptoms of cerebral ischemia and experienced stroke at least once; 3) digital subtraction angiography (DSA) suggested severe cerebrovascular stenosis or occlusion of ICA or MCA; 4) without contraindication for MRI. The inclusion criteria for healthy volunteers were 1) without a history of ischemic attack or stroke; 2) healthy on the physical examination. Patients with hypertension or diabetes were excluded. All protocols used in this study were approved by the ethics committee at Beijing University and written informed consent was obtained from all participants.

OEF-MRI Protocol

MRI examinations were performed three days preoperatively and 2-4 months postoperatively in all subjects. All images were obtained using a 3T MRI scanner (GE Healthcare, Milwaukee, USA) with a commercial 8-channel head coil. All patients received routine clinical pulse sequences including axial T1 fluid-attenuated inversion recovery (FLAIR), axial T2-weighted FLAIR and diffusion weighted imaging (DWI) sequences. Then arterial spin labeling (ASL) or perfusion-weighted imaging (PWI) was performed to obtain the hemodynamic information of cerebral blood flow (CBF) (14). The perfusion study consisted of multiple measurements (50 at 1.5-second intervals) after a standard injection of 20 mL gadodiamide (Gd-DTPA-BMA) with a flow rate of 3 mL/s. CBF maps were calculated from the raw data provided by the manufacturer on the workstation. Alternatively, CBF was measured with ASL by using intravascular water as endogenous contrast agent with the parameters as follow: repetition time (TR) = 3000 ms, echo time (TE) = 3.4 ms, flip angle = 20°, matrix = 128×128, number of excitation (NEX) =1, slice thickness = 8.0 mm and gap = 2 mm.

Furthermore, a specially designed sequence-gradient echo sampling spin echo (GESSE) was performed to provide the information of OEF. GESSE was a multi-echo gradient and spin echo magnetic resonance imaging sequence reported previously (1). The imaging parameters used in GESSE were: TR = 1500 ms, TE = 56 ms, electron capture 62.5 kHz, matrix = 128 × 128, field of view = 240 mm × 240 mm, slice thickness = 7.5 mm, NEX = 4, and scanning time = 12 min plus 55 s (23). Thirty-two echoes with an echo spacing of 1.5 milliseconds were acquired and 32 images were obtained to be used as raw data for calculating OEF. Only one axial slice above the corpus callosum was acquired in this study. The signal interference between two adjacent slices, potential crosstalk and bone-gas interface artifact could be minimized. The MRI protocols remained the same for the initial and follow-up MRI examination.

The healthy volunteers firstly underwent routine MRI to ensure there was no abnormality in their brains. GESSE sequence was performed to obtain the normal value of OEF.

Data Analysis

A theoretical signal model, which describes the signal dephasing phenomena in the presence of deoxyhemoglobin, was used for post processing the acquired images and a quantitative measurement of OEF was obtained (2). This was achieved by the software developed in house. Estimation of OEF has been described somewhere else before (23). After the OEF map was generated, six region of interests (ROIs), which equally divided two hemispheres were used for the estimates of OEF. These ROIs were placed in the anterior, middle and posterior parts of bilateral hemispheres, which corresponded to the territory of anterior cerebral artery, middle cerebral artery, and posterior cerebral artery, respectively (Figure 1) (23). The size of ROI ranged from 220-350 mm^2, and voxels with low signal to noise ratio resulted from artifacts were avoided in the measurement. To better match the ROI and ischemic region, the location and size of some ROIs were adjusted mildly by a radiologist.

The OEF values of normal controls were obtained from 9 healthy volunteers. The upper limit of normal OEF range was defined as mean + 2 SDs of the controls. If the OEF value of the ROI in the patient's brain was higher than the upper limit, it was considered to be elevated and the region was assumed to have misery perfusion. CBF maps were also generated using the software on the workstation. The perfusion status of the brain was determined by an experienced radiologist. The relative CBF (rCBF) in each ROI was defined as the ratio of CBF in the ischemic hemisphere to that in the contralateral hemisphere. Regions with abnormal OEF were defined and the changes of postoperative OEF relative to baseline OEF were calculated.

Statistical Analysis

Data were expressed as mean ± SD. Comparison was conducted by paired *t* test and $p<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Clinical Characteristics of the Subjects

Among the 9 patients undergoing cerebrovascular surgery, 6 were male and 3 were female, with ages ranging from 42 to 73 (mean age, 59.1 years). The diagnosis and surgical treatment of these patients are presented in Table I. Three patients were treated with a stent in the carotid artery and one patient in the vertebral artery. The remaining five patients underwent superficial temporal artery-middle cerebral artery (STA-MCA) bypass. Normal volunteers including 4 men and 5 women (mean age 59 years) were recruited from the relatives of the hospital staff.

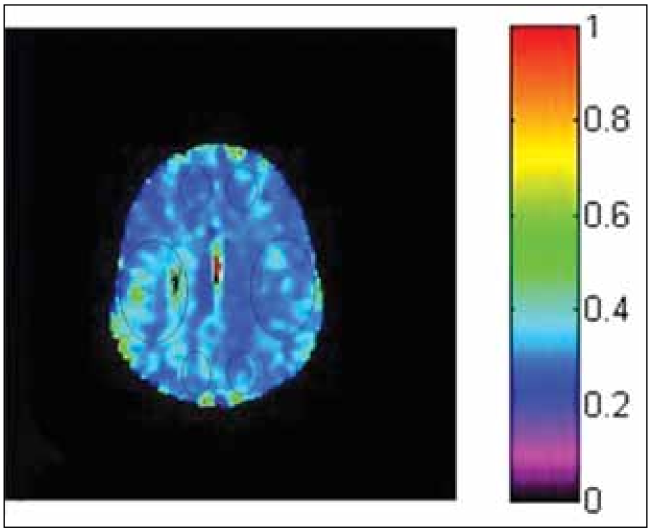

Figure 1: Representative ROI placement for OEF measurement in the study, shown on the OEF map from a patient. Each ROI was placed in the anterior, middle and posterior part of bilateral hemispheres, which corresponded to the territory of anterior cerebral artery, middle cerebral artery, and border zone of middle cerebral artery and posterior cerebral artery respectively. CBF was measured in the same way.

Median time from surgery to follow-up MRI was 13.5 weeks. MRI assessment at follow-up found no restenosis in the stents and the anastomotic orifice was apparent in all patients undergoing STA-MCA bypass surgery.

Normal OEF Assessment by MRI

A total of 54 ROIs were selected from healthy volunteers, and OEF values from six different cerebral vascular zones in each volunteer were compared. No significant difference was detected among different zones ($F = 2.117$, $p = 0.079$). The normal range of OEF measured in the controls was 0.257–0.349 for the whole brain.

Preoperative Hemodynamic Assessment

A total 54 ROIs were selected from the patients to calculate OEF preoperatively (Table II). Among them, 16 ROIs presented an elevated OEF, compared with the upper limit of normal range of OEF, including 13 ROIs in the ipsilateral side of surgical treatment and 3 ROIs in the contralateral side. Eight patients with internal carotid artery (ICA) or middle cerebral artery (MCA) stenosis/occlusion were detected as elevated OEF including 8 ROIs in ipsilateral MCA territory, 2 ROIs in ipsilateral anterior cerebral artery (ACA) territory, one ROI in ipsilateral posterior cerebral artery (PCA) territory, and 3 ROIs on the contralateral side. The rCBF values of these ROIs ranged from 0.2 to 0.6. One patient with vertebral stenosis was characterized with an elevated OEF in the ROIs of ipsilateral MCA and PCA territory and the rCBF value of ROIs was 0.6 in ipsilateral PCA region and 1.0 in ipsilateral MCA region.

Postoperative Hemodynamic Change

No new infarction was found during the follow-up period. Of the 16 ROIs with elevated OEF preoperatively, OEF values of 15 ROIs decreased to normal level, while OEF value of one ROI remained a high level in patient 8. The 3 ROIs which presented an elevated OEF on the contralateral side preoperatively decreased to normal level at follow-up MRI. The rCBF value increased to 0.8-1.3 in the ROIs with preoperatively elevated OEF. The rCBF value of the ROI with postoperative elevated OEF in patient 8 reached to 0.8.

Preoperative and postoperative OEF values of the elevated ROIs were 0.367 ± 0.012 and 0.316 ± 0.025, respectively. Paired *t*-test showed that there was a significant difference between them ($t = 7.685$, $p < 0.001$) (Figure 2).

By setting the cut-off value as 0.365, 16 ROIs with elevated preoperative OEF were divided into two groups: low-OEF

Table I: Patients' Clinical Data

Patient No.	Gender	Age	DSA findings	Surgical treatment
1	M	68	Severe stenosis in siphon segment of left ICA complicated with aneurysm	Left ICA stent
2	M	61	severe stenosis in siphon segment of right ICA	Right ICA stent
3	M	58	Severe ostial left ICA stenosis	Left ICA stent
4	M	49	Severe right VA stenosis, left VA occlusion	Right VA stent
5	F	45	Right MCA Occlusion	Right STA-MCA bypass
6	F	68	Left ICA Occlusion	Left STA-MCA bypass
7	M	42	Left MCA occlusion	Left STA-MCA bypass
8	M	68	Severe left ICA stenosis, left ACA and MCA stenosis	Left STA-MCA bypass
9	F	73	Multiple intracranial vascular stenosis in the right side	Right STA-MCA bypass

Table II: The Oxygen Extraction Fraction (OEF) and Relative Cerebral Blood Flow (rCBF) in Patients Undergoing Cerebrovascular Surgery Pre- and Post- Operatively

		OEF		average rCBF	
	ROI	pre-surgery	post-surgery	pre-surgery	post-surgery
Patient 1	1	**0.368**	0.293	0.59	1.1
	2	**0.375**	0.278		
	3	**0.367**	0.293		
	4	*0.361*	0.305		
	5	0.309	0.276		
	6	*0.364*	0.339		
Patient 2	1	0.306	0.301	0.67	1.3
	2	0.321	0.306		
	3	*0.362*	0.341		
	4	**0.374**	0.284		
	5	**0.387**	0.323		
	6	0.338	0.333		
Patient 3	1	0.289	0.298	0.28	1.37
	2	**0.368**	0.294		
	3	0.271	0.281		
	4	0.278	0.293		
	5	0.295	0.287		
	6	0.278	0.282		
Patient 4	1	0.286	0.287	0.54	0.92
	2	0.331	0.318		
	3	0.285	0.305		
	4	0.294	0.280		
	5	0.355	0.343		
	6	**0.353**	0.304		
Patient 5	1	0.292	0.255	0.36	0.83
	2	0.303	0.271		
	3	0.319	0.296		
	4	0.304	0.299		
	5	**0.352**	0.324		
	6	0.334	0.322		

Table II: Cont.

		OEF		average rCBF	
	ROI	pre-surgery	post-surgery	pre-surgery	post-surgery
Patient 6	1	0.274	0.277	0.6	0.8
	2	**0.362**	0.331		
	3	0.299	0.299		
	4	0.275	0.290		
	5	0.290	0.262		
	6	0.306	0.279		
Patient 7	1	0.261	0.296	0.62	0.8
	2	**0.361**	0.335		
	3	0.334	0.344		
	4	0.272	0.299		
	5	0.341	0.299		
	6	0.326	0.338		
Patient 8	1	0.274	0.296	0.76	1.2
	2	**0.399**	**0.368**		
	3	0.336	0.327		
	4	0.27	0.272		
	5	0.319	0.329		
	6	0.299	0.315		
Patient 9	1	0.275	0.259	0.5	1.1
	2	0.297	0.285		
	3	0.298	0.273		
	4	0.297	0.289		
	5	**0.368**	0.307		
	6	0.321	0.283		

*** ROI,** *region of interest. The number in bold represents elevated OEF in ischemic side and the italics represents elevated OEF in contralateral side.*

group with OEF ranged from 0.350 to 0.365 and high-OEF group with OEF ranged from 0.365 to 0.400. Each group included 8 ROIs, respectively. OEF value decreased by 0.031 ± 0.020 after operation in the low-OEF group, while decreased by 0.071 ± 0.015 in the high-OEF group. The OEF change was significantly different between the two groups (t = 4.541, p = 0.001).

DISCUSSION

After the onset of cerebral ischemia, the oxygen extraction fraction (OEF) is elevated in an effort to compensate for the reduced cerebral blood flow (CBF) to preserve neuronal function (18, 23). In this study, we analyzed the hemodynamic changes quantitatively in patients with cerebrovascular stenosis or occlusion before and after vascular surgery by combing OEF and MRI. Our results showed that OEF values in some ischemic brain regions were elevated compared with that in healthy volunteers and most of these elevated OEF values could decrease to normal range after surgery, indicating patients with severe cerebrovascular stenosis or occlusion disease could receive benefits from revascularization. Besides, our results confirm that MRI technique could be applied in evaluating cerebral hemodynamic status.

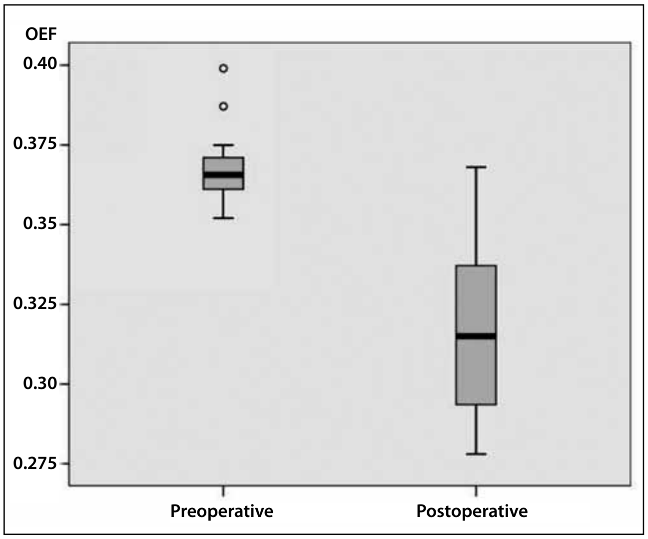

Figure 2: Graph shows the effect of vascular surgery on OEF in ROIs with misery perfusion. Whiskers mark the 10th and 90th percentiles, and boxes are bounded by the 25th and 75th percentiles.

Previous studies suggested extra-cranial to intracranial (EC-IC) bypass will be cost-effective in patients suffering symptomatic carotid occlusion accompanied with OEF increasing (13, 16). Elevated cerebral OEF value meant stage II hemodynamic failure, which could play a vital role in patients' selection (4). Thus, the detection of elevated OEF region is important and necessary in patient's examination. In our patients, elevated OEF value was detected in the regions of ipsilateral stenosis or occlusive vessels (Figure 3) (5), suggesting that OEF-MRI could become a potential method used in selecting patients suffering from intracranial stenosis or occlusive disease as well as benefiting from revascularization. Besides the ROIs of ipsilateral to the stenosis/occlusive vessels, 3 ROIs of contralateral to the symptomatic side were found to have misery perfusion as well (Figure 4). This finding was consistent with a previous study (9). and might have resulted from the 'steal phenomenon' (12,19). Patients with ICA or MCA stenosis/occlusion possessed a decreased CBF value in the ischemic hemisphere compared with that in the contralateral side. However, the value of rCBF indicated great variation and ranged from 0.2 to 0.6. Since the blood flow is directed from the contralateral hemisphere to the compromised ipsilateral hemisphere (21), using the preoperative contralateral hemisphere as a reference may lead to an underestimation of rCBF. Under this condition, OEF value is considered to be a more accurate index for the assessment of hemodynamic impairment (20). Our results suggested that OEF would be more sensitive to evaluate cerebral hemodynamic changes.

Postoperative MRI in the follow-up period in our study showed a significant change in stent and bypass, indicating that the elevated OEF value in the regions was decreased postoperatively (Figure 3, 4). The OEF that decreased in the ischemic brain regions was accompanied by restoration of blood flow. An exception was occurred in patient 8, who showed one ROI with postoperative elevated OEF and rCBF value of 0.8. As the patient had severe left ICA stenosis, left ACA and MCA stenosis, we speculated that this was because brain ischemia in this patient was too severe to be corrected by bypass surgery. In summary, the comparison between preoperative and postoperative OEF indicated a significant hemodynamic change after surgery. The hemodynamic improvement occurred in both ipsilateral hemisphere and contralateral hemisphere. This result was in well accordance with previous reports based on PET studies (9). Furthermore, our study showed that ischemic regions with

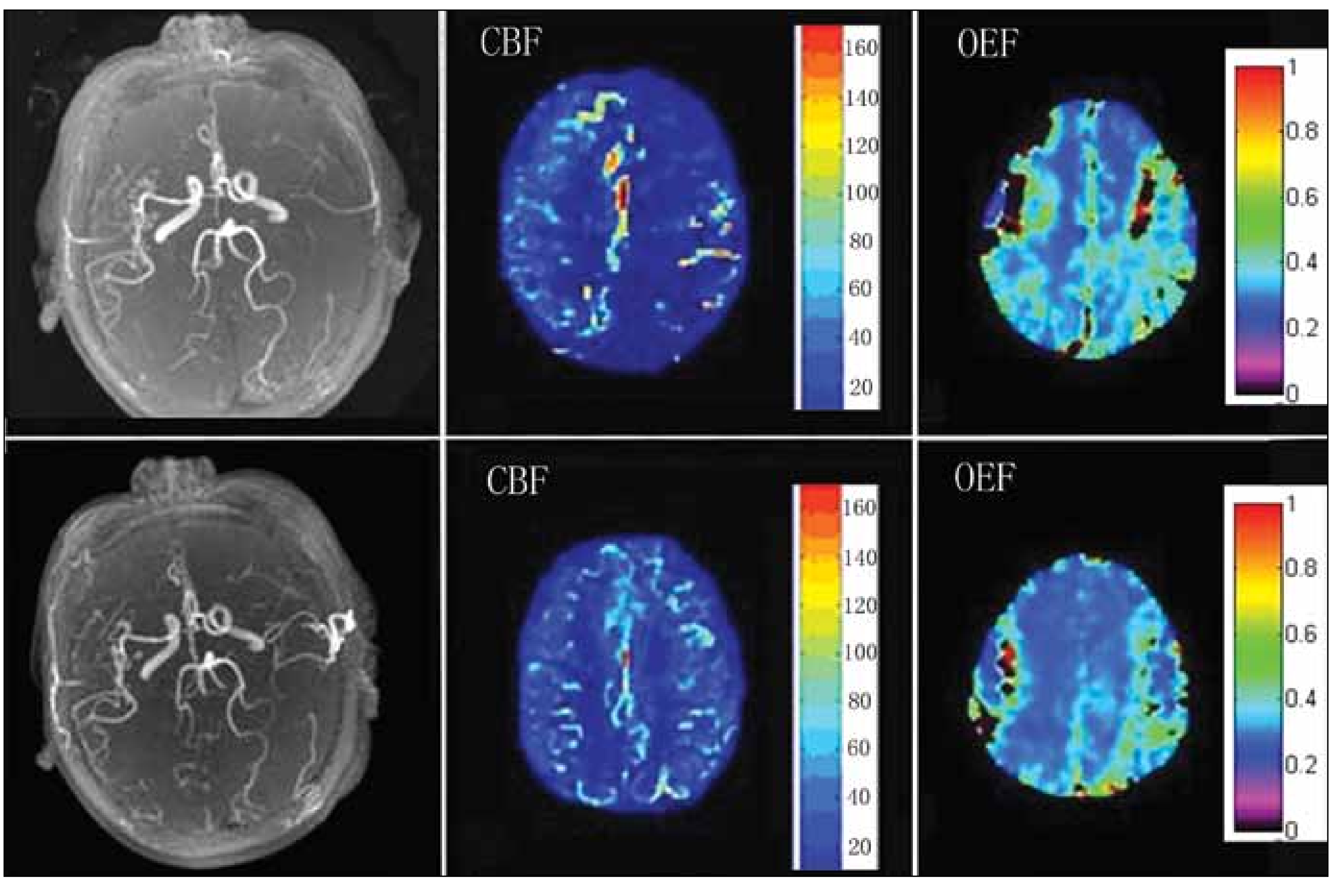

Figure 3: Preoperative (superior line) and postoperative (inferior line) hemodynamic assessment in Patient 7. Preoperative **MRA** showed left MCA occlusion. **CBF** map showed markedly reduced blood flows in the left hemisphere, and **OEF** is significantly elevated (0.361) in the regions of left MCA. After STA-MCA bypass, increased **CBF** is found in the left hemisphere, and **OEF** decreases in regions of MCA territory.

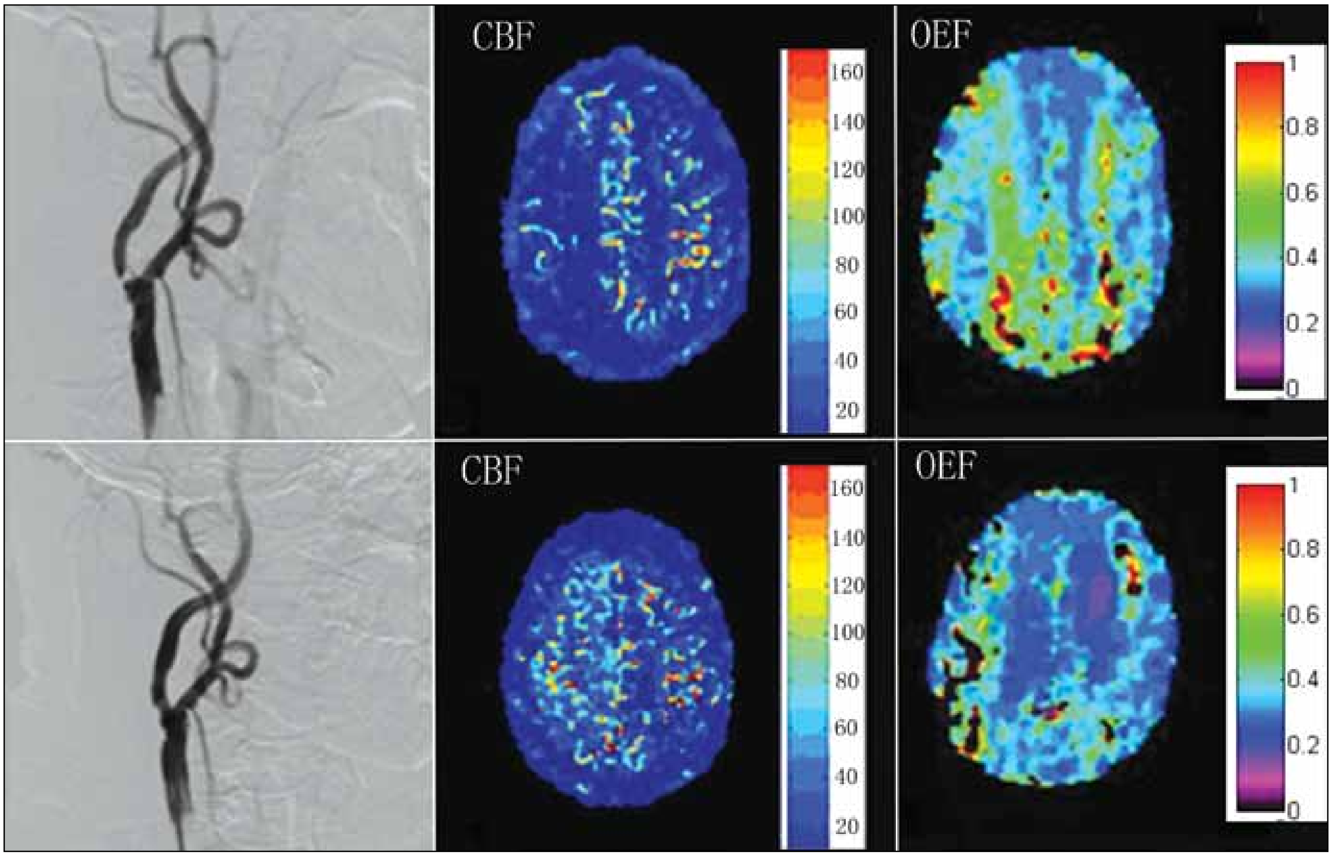

Figure 4: Preoperative and postoperative hemodynamic assessment in Patient 2. Preoperative **DSA** shows severe right ICA stenosis. **CBF** is markedly reduced compared with the contralateral hemisphere, and **OEF** is increased in most regions of right hemisphere as well as in the posterior left hemisphere. After stenting, ICA appears patent, the right hemisphere is hyperperfused, and **OEF** decreases to normal level.

more preoperative elevated OEF would benefit more from the revascularization (10,19). Thus, improvement of OEF might bring the patients opportunities in revascularization surgery. Our results provided the evidence of hemodynamic improvement after revascularization, but it still could not provide evidence for allowing all patients with occlusive disease to develop revascularization.

The present study also has several limitations. Firstly, paramagnetic sources other than deoxyhemoglobin can induce an additional signal-intensity loss in MRI, and thus might lead to an unavoidable error in the measurement of OEF in the local brain. This phenomenon was not uncommon in the postoperative brain. Using titanic nails often leads to a metal artifact on MRI, which would be more severe for OEF-MRI. Secondly, a known hematocrit value is needed to obtain a quantitative measurement of cerebral blood oxygen saturation. We established an analytic model of a constant hematocrit of 0.42, which could contribute directly to OEF value estimation to avoid errors induced by the inaccuracy of hematocrit. Under the pathologic conditions of brain ischemia, the error might cause underestimation of OEF value in the ischemic brain tissue, which might result in hematocrit decreasing in the local small vessel in certain extent (24). Thirdly, we have used an atlas-based segmentation of vascular territories in to ACA, MCA and posterior distributions. Vascular territories might have altered size and geometry in patients with severe cerebrovascular disease.

In conclusion, the preoperative hemodynamic impairment of patients with severe cerebrovascular disease could be manifested as elevated OEF by using the OEF-MRI technique. An improvement of hemodynamic status was found in these patients after revascularization. OEF-MRI might play an important role in the selection of patients for surgical intervention, and could be applied in quantitative evaluation of the therapeutic effect in cerebral ischemia treatment.

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