Prediction of Infarction in Acute Cerebral Ischemic Stroke by Using Perfusion MR Imaging and ^{99m}Tc-HMPAO SPECT

Ho Cheol Choe, Sun Joo Lee, Jae Hyoung Kim

Purpose : We investigated the predictive values of relative CBV measured with perfusion MR imaging, and relative CBF measured with SPECT for tissue outcome in acute ischemic stroke.

Material and Methods : Thirteen patients, who had acute unilateral middle cerebral artery occlusion, underwent perfusion MR imaging, and ^{99m}Tc-HMPAO SPECT within 6 hours after the onset of symptoms. Lesion-to-contralateral ratios of perfusion parameters were measured, and best cut-off values of both parameter ratios with their accuracy to discriminate between regions with and without evolving infarction were calculated.

Results : Mean relative CBV ratios in regions with evolving infarction and without evolving infarction were 0.58 ± 0.27 and 0.99 ± 0.17 ($p < 0.001$), and mean relative CBF ratios in those regions were 0.41 ± 0.22 and 0.71 ± 0.14 ($p < 0.001$). The best cutoff values to discriminate between regions with and without evolving infarction were estimated to be 0.80 for relative CBV ratio and 0.56 for relative CBF ratio. The sensitivity, specificity and efficiency of each cutoff value were 80.6, 87.5, 82.7% for relative CBV ratio, and 72.2, 75.0, 73.0% for relative CBF ratio ($p > 0.05$ between two parameters).

Conclusion : Measurement of relative CBV and relative CBF may be useful in predicting tissue outcome in acute ischemic stroke.

Index words : Brain, blood flow
Brain, ischemia
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Introduction

The role of neuroimaging in acute ischemic stroke is not only an early detection of ischemia, but also an identification of viability of ischemic tissue. Recently, by using combined diffusion and perfusion MR imaging, the mismatch between lesion extents on both imagings has

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been considered as an estimate of ischemic penumbra (1, 2). However, we still need quantitative criteria concerning the tissue viability because the mismatch sometimes goes on to infarction and sometimes does not, probably depending on the individual variability of hemodynamic status (i.e., the amount of residual perfusion). Therefore, interests have been focused on identification of the tissue viability by measuring the perfusion parameters such as cerebral blood flow (CBF) and cerebral blood volume (CBV) at the acute stage of ischemic stroke. Definite quantitative criteria for CBF and CBV to predict the tissue outcome have not yet been established. Although a few studies using positron emission tomography (PET), which is referred to as a gold standard for perfusion measurement, have been conducted to investigate the change of CBF and CBV in acute ischemic stroke (3, 4), it still can not be useful in emergent evaluation of cerebral perfusion because of limited availability.

Single-photon emission CT (SPECT) and perfusion MR imaging, which can measure relative CBF and relative CBV, respectively, are clinically more accessible methods than PET. A few studies of SPECT have been conducted to determine the quantitative threshold of relative CBF for prediction of tissue outcome in acute ischemic stroke, and comparably similar data have been reported among those studies (5–8). Perfusion MR imaging has been increasingly utilized to measure the various perfusion parameters in acute ischemic stroke and the size of relative CBV abnormality was reported to correlate best with that of final infarction (2, 9). However, comparative studies between relative CBF measured with SPECT and relative CBV measured with perfusion MR imaging have been rarely conducted for predictive values of tissue outcome (10, 11).

In our study, we performed both SPECT and perfusion MR imaging in patients with acute middle cerebral artery occlusion within 6 hours after the onset of symptoms. Relative CBF was measured with SPECT, and relative CBV was calculated with perfusion MR imaging. We investigated the predictive values of relative CBF and relative CBV for tissue outcome by calculating the thresholds of these parameters with their accuracy.

Materials and Methods

Patients

Forty-four consecutive patients underwent perfusion MR imaging within 6 hours after the onset of symptoms of acute middle cerebral artery occlusion during a period of three years. Of these 44 patients, 13 patients, who had unilateral occlusion of M1 segment (proximal horizontal segment of middle cerebral artery) and underwent perfusion MR imaging together with SPECT in less than 20 minute time interval between the two examinations, were included in this study. They had only conservative treatment with or without intravenous heparin therapy (n = 9), or failed intraarterial thrombolysis (n = 4) during the acute stage of stroke were selected for this study.

Perfusion MR imaging was performed from 2 to 6 hours (mean, 3.9 hours) after the onset of symptoms in these 13 patients. Occlusion of M1 segment was determined by MR angiography which was included in our MR imaging protocol for acute ischemic stroke. Patients were 30–81 years old (mean, 56 years; 7 men and 6 women).

Imaging Studies

MR examinations were performed on a 1.5T 63SP system (Siemens, Erlangen, Germany) with our acute stroke protocol (turbo spin-echo T2-weighted imaging, axial spin-echo T1-weighted imaging, MR angiography, dynamic contrast-enhanced T2*-weighted imaging for perfusion-weighted imaging, and postcontrast T1-weighted imaging in sequence). The imaging parameters were 3500–5000/90 (repetition time msec/echo time msec) for T2-weighted imaging and 550/14 for T1-weighted imaging. Section thickness was 5–6 mm and matrix number was 192×256. MR angiography was performed around the Circle-of-Willis with a standard 3D time-of-flight sequence (38/7, 15° flip angle, 64 mm slab thickness and 192×256 matrix). Total imaging and processing time was approximately 17 minutes. The total scan time, including patients transfer to and from the table, patient positioning and coil tuning, was within 25 minutes.

Dynamic contrast-enhanced T2*-weighted imaging was performed with a conventional gradient-echo sequence (40/26, 10° flip angle, 64×128 matrix, 5–

6 mm slice thickness, 3.8 sec acquisition time). Single-section 17–22 dynamic images were obtained at the level of the basal ganglia, at which level the largest infarction is usually detected on T2-weighted images. After acquisition of the first three images, gadodiamide (Omniscan, 0.2 mmol/kg) was administered via the forearm vein as a bolus within 5 seconds, followed by a flush of 30 ml saline. The total imaging time was approximately 60 seconds after initiation of bolus injection.

All dynamic MR images were transferred via Ethernet to a personal computer after image aquisition. Relative CBV and TTP maps were created by using inhouse software as follows. According to the indicator dilution theory, non-linear regression method was used to fit a gamma-variate function to the contrast material concentration versus time curve on a pixel-by-pixel basis, under the assumption of exponential relationship between the relative signal reduction and the contrast material concentration (12). Then, relative CBV was calculated by numerical integration of the area under the concentration-time curve (i.e., CBV = $\int C(_t)dt$). The time-to peak (TTP) was calculated as the time for contrast material to reach the highest concentration (13).

A Siemens MULTI-SPECT3 (Chicago, IL) was used for cerebral blood flow (CBF) imaging. Patients received 28–35 mCi (1036–1295 MBq) of ^{99m}Tc-HMPAO within 20 minutes before or after MR imaging. Scanning (20 minutes on average acquisition time) was performed within 2 hours after tracer injection depending on the patient's condition. Images were reconstructed in 128 × 128 matrix, 410 mm field-of-view and 5 mm slice thickness in transverse, sagittal and coronal planes using Butterworth filtered backprojection.

Follow-up MR imagings were performed at various times from 1 to 28 days (mean, 7.2 days) after the onset of symptoms. Abnormal hyperintense area on T2-weighted image was considered as eventual infarction.

Image Analysis

According to the findings of initial T2-weighted images, initial TTP maps and follow-up images, affected MCA territories were divided into regions with evolving infarction (area of final infarction), and regions without evolving infarction (area of TTP abnormality minus that of final infarction) based on visual analysis (Fig. 1a-c). Thereafter we placed variable-sized region-of-interests (ROIs) symmetrically in both affected and contralateral hemispheres on relative CBV maps (Fig. 1d). We made an effort to place two ROIs in regions with evolving infarction and the other two ROIs in regions without evolving infarction, but it depended on the extent of infarctions. Thus all four ROIs were placed in regions with evolving infarction when the extent of infarction matched that of TTP abnormality. Each ROI included 120–240 pixels, which corresponded to 3–6 cm^2 in size. Care was taken to include cortical areas as much as possible in a given ROI, but some subcortical white matter was inevitably contained. Using the contralateral hemisphere as reference, lesion-to-contralateral relative CBV ratios (i.e., relative CBV of a ROI in the affected vascular territory divided by that of corresponding contralateral ROI) were calculated.

For comparative analysis of relative CBV and relative CBF, we selected two consecutive sections of SPECT images, the imaging planes of which fitted best that of relative CBV map, because of unavailability of automated MR-SPECT coregistration technique. Symmetric mirror ROIs used above for measurement of relative CBV ratio were copied on each of the selected SPECT images (Fig. 1e). Owing to unequal dimension between SPECT image and CBV map, we adjusted slightly the spatial location of ROIs on SPECT images. Lesion-to-contralateral relative CBF ratios (i.e., radioisotope activity in a ROI of the affected vascular territory divided by that of corresponding contralateral ROI) were then calculated on the two sections and averaged for comparison with relative CBV ratios.

Statistical Analysis

Differences of relative CBV and relative CBF ratios between regions with and without evolving infarction were examined by student t test. Univariate discriminate analysis was performed to obtain the best cutoff values of each perfusion parameter to discriminate between regions with evolving infarction and without evolving infarction. On the basis of the best cutoff values, the sensitivity (true positive prediction of infarction), specificity (true positive prediction of non-infarction) and efficiency (true positive prediction of either infarction or non-infarction) were calculated. Differences of the sensitivity, specificity and efficiency between relative CBV and relative CBF were examined by χ^2 test. Statistical computations were performed with the SPSS

statistical software package (SPSS, Chicago, IL), and the level of statistical significance was defined as $p < 0.05$.

Results

The overall results of patients and hemodynamic data are summarized in Table 1. Thirty-six ROIs were placed in regions with evolving infarction and 16 ROIs were in regions without evolving infarction. Mean relative CBV ratios in regions with and without evolving infarction were 0.58 ± 0.27 and 0.99 ± 0.17, respectively ($p < 0.001$) (Fig. 2). Mean relative CBF ratios in regions with and without evolving infarction were 0.41 ± 0.22 and 0.71 ± 0.14, respectively ($p < 0.001$) (Fig. 3).

From discriminate analysis, the best cutoff values to discriminate between regions with and without evolving infarction were estimated to be 0.80 for relative CBV ratio and 0.56 for relative CBF ratio (Fig. 2 & 3). The sensitivity, specificity and efficiency of each cutoff value to predict the tissue outcome were 80.6, 87.5, 82.7% for

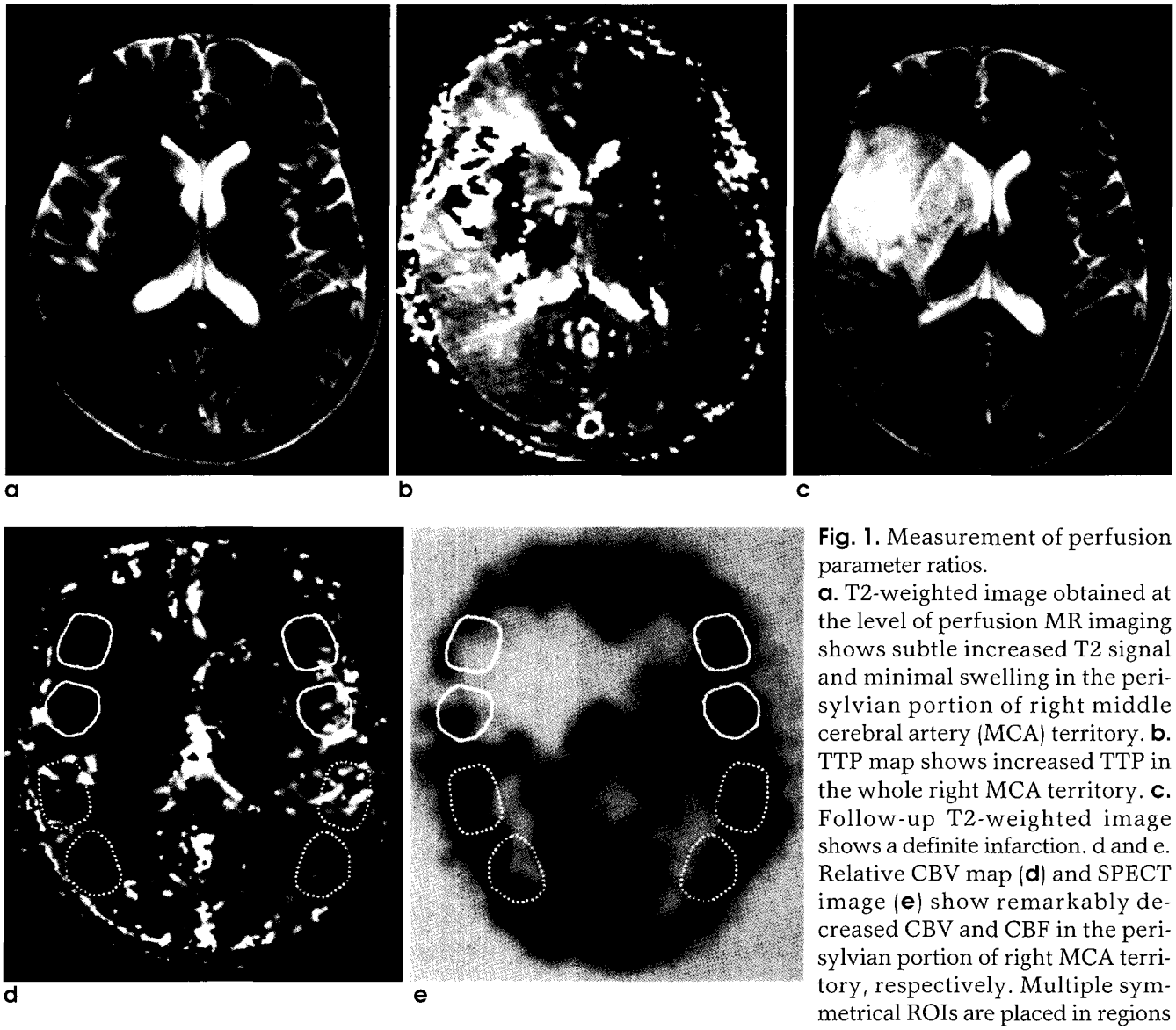

Fig. 1. Measurement of perfusion parameter ratios.
a. T2-weighted image obtained at the level of perfusion MR imaging shows subtle increased T2 signal and minimal swelling in the perisylvian portion of right middle cerebral artery (MCA) territory. **b.** TTP map shows increased TTP in the whole right MCA territory. **c.** Follow-up T2-weighted image shows a definite infarction. d and e. Relative CBV map (**d**) and SPECT image (**e**) show remarkably decreased CBV and CBF in the perisylvian portion of right MCA territory, respectively. Multiple symmetrical ROIs are placed in regions with evolving infarction (solid line in right hemisphere) and without evolving infarction (dotted line in left hemisphere) for measurement of relative CBV and CBF ratios.

relative CBV ratio, and 72.2, 75.0, 73.0% for relative CBF ratio. Relative CBV ratio was slightly superior to relative CBF ratio in predicting tissue outcome, however, the sensitivity, specificity and efficiency were not statistically significantly different between the two perfusion parameters.

Discussion

Recently, combined perfusion and diffusion MR imaging has been utilized in an attempt to discriminate between the tissues which proceed to infarction and tissues which do not. Perfusion-diffusion mismatch on MR imaging has been reported to be correlated with reversible ischemic tissue (14-16). However, the tissue with a mismatch sometimes goes on to infarction and sometimes does not, probably depending on the individual variability of hemodynamic status (15, 17). Furthermore, there are no absolute threshold for apparent diffusion coefficient that predicts tissue outcome

Table 1. Summary of Findings in Patients

Case	Age(y) /Sex	Time to Initial MRI (hr)	Regions with Evolving Infarction (N = 36) rCBV ratio	rCBF ratio	Regions without Evolving Infarction (N = 16) rCBV ratio	rCBF ratio
1	55/M	4	0.38	0.23	1.14	0.51
			0.75	0.42	1.05	0.55
2	49/F	6	0.56	0.61	1.00	0.92
			0.34	0.30	0.84	0.86
3	65/M	4	0.32	0.26	0.87	0.52
			0.28	0.14		
			0.57	0.40		
4	81/F	5	0.51	0.63		
			1.00	0.47		
			1.33	0.73		
			0.84	0.82		
5	25/F	3.5	0.43	0.43	0.87	0.52
			0.21	0.30	1.01	0.79
6	78/M	3	0.55	0.10	0.85	0.58
			0.63	0.09		
			0.21	0.33		
7	30/F	5.5	0.34	0.17	0.67	0.79
			0.38	0.14		
			0.40	0.38		
8	37/F	4.5	0.44	0.23	0.94	0.66
			0.67	0.31	1.08	0.76
9	66/M	3	0.65	0.18		
			0.53	0.16		
			0.68	0.21		
			0.76	0.56		
10	51/F	4	0.62	0.58	1.05	0.60
			0.46	0.46		
			0.84	0.60		
11	70/M	2	0.24	0.44	0.74	0.87
			0.26	0.40		
			0.70	0.74		
12	71/M	3.5	0.41	0.20	1.30	0.84
					1.18	0.75
					1.17	0.80
13	51/M	3.5	0.67	0.47		
			1.08	0.84		
			1.02	0.55		
			0.99	0.76		

rCBF = relative cerebral blood flow; rCBV = relative cerebral blood volume.

(18), and no linear relationship between the decreased apparent diffusion coefficient and degree of eventual ischemic injury (19, 20). Even the tissue with diffusion abnormality was reported to be salvaged with successful thrombolysis (21, 22). Therefore, tissue reversibility can not be evaluated by diffusion abnormality alone. Independent quantitative assessment of perfusion parameters is still informative for predicting the tissue outcome.

Various perfusion-related parameters have been proposed to assess acute ischemic stroke in terms of the extent and severity of perfusion abnormality. Although the significance of each parameter is still a matter of debate, relative CBF and relative CBV have been studied the most, using SPECT and perfusion MR imaging, respectively (6, 8, 10, 11, 23). Among the patients in our study, relative CBF and relative CBV of regions with evolving infarction were significantly lower than those of regions without evolving infarction, which are consistent with previous results (10, 11).

The significant differences of relative CBF and relative CBV between regions with and without evolving infarction suggest that threshold values of each parameter for predicting tissue outcome can be estimated. Previous studies have reported relative CBF ratios in a range of 0.52–0.7 as threshold values for development of infarction (7, 8, 10). Threshold values for relative CBV ratios have been reported to be 0.85–0.87 (10, 11). Threshold values of the two parameters in our study are similar to the previous results, although perfusion MR imaging and SPECT were performed with shorter time interval than in the previous studies, allowing more precise comparison of the two parameters.

Based on visual analysis, the extent of relative CBV abnormality has been reported to correlate best with that of final infarction, compared with relative CBF and mean transit time (2, 9). In our study, the sensitivity, specificity and efficiency of the threshold value of relative CBV to predict tissue outcome were slightly higher than those of relative CBF, but the differences were not

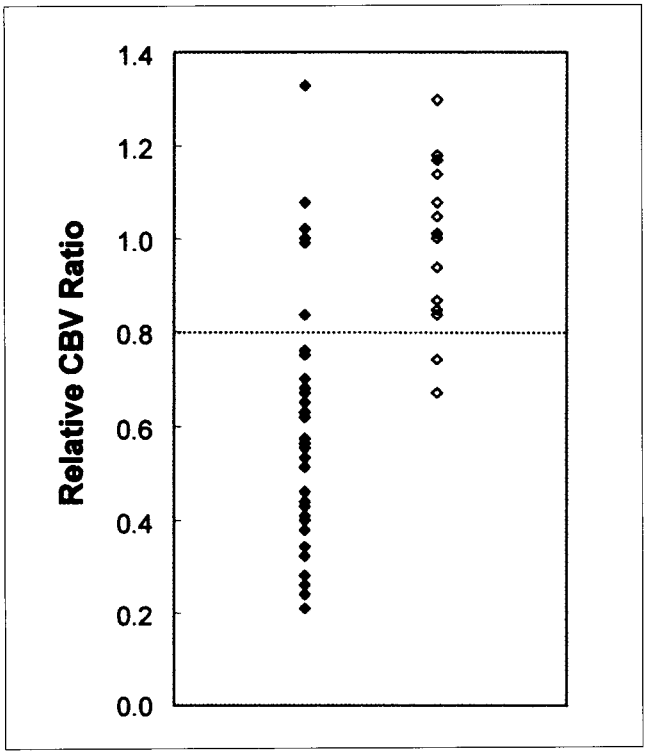

Fig. 2. Scatterplot shows relative CBV ratios for regions with evolving infarction (◆) and without evolving infarction (◇). The best cutoff value of relative CBV ratio to discriminate between regions with and without evolving infarction is 0.80 (indicated by horizontal line).

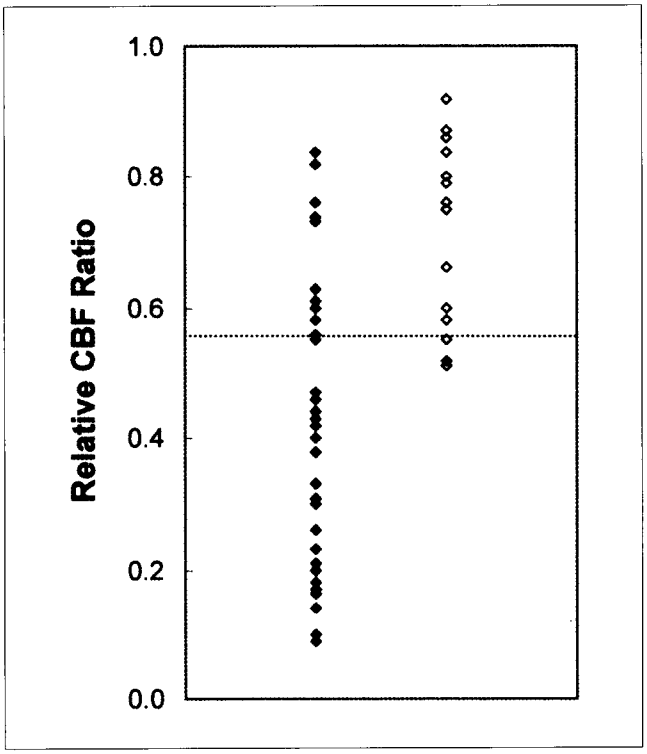

Fig. 3. Scatterplot shows relative CBF ratios for regions with evolving infarction (◆) and without evolving infarction (◇). The best cutoff value of relative CBF ratio to discriminate between regions with and without evolving infarction is 0.56 (indicated by horizontal line).

statistically significant. Definite criteria for all these perfusion-related parameters mentioned above to predict the tissue outcome have not yet been established. Further studies with a greater number of patients are needed.

Unexpectedly large infarctions were found, compared with the extent of initial perfusion abnormalities, on follow-up images of two patients in our study. Relative CBF was slightly low and relative CBV was near-normal in the substantially large areas of the affected vascular territories. Thus, those areas were initially considered not to proceed to infarction. Secondary ischemic events such as clot progression, clot fragmentation and migration, new emboli could not be excluded. However, we can not determine whether the infarction was caused by secondary ischemic insults or initial ischemic insult alone with failure of collateral development.

Our study has several methodological and technical limitations. First limitation is that our study was not conducted for patients with successful thrombolytic therapy. The study was based on a population of patients who had only conservative therapy or failed thrombolytic therapy. Threshold values of perfusion parameters in the tissue salvageable with thrombolytic therapy can be lower than those obtained in the tissue treated with conservative therapy. Therefore, further study including patients with early successful thrombolysis will provide more practical quantitative data which help to guide the selection of patients who will benefit from thrombolytic therapy. Second, only relative perfusion parameter values were provided and therefore the contralateral values were considered as normal controls. However, the contralateral hemisphere may be affected by ischemic insult. Unfortunately, absolute parameter values can not be measured currently with perfusion MR imaging, although deconvolution technique of arterial input function provides more reliable data than the method used in our study. Third, coregistration between CBV map and SPECT image was not utilized. We selected two consecutive SPECT images, which fit best the CBV map, by visual determination. Thus, regional comparison between CBV map and SPECT image may not be sufficiently accurate. Fourth, only single section can be evaluated with conventional dynamic contrast-enhanced T2*-weighted imaging technique. Thus, concerns about the reliability of data obtained at single section without covering the whole region of ischemia may be raised. However, we think that single section perfusion MR imaging can provide useful hemodynamic information in a homogeneous group of patients with M1 segment occlusion as in our study, because the imaging plane at the level of the basal ganglia covers usually the largest ischemic region in case of M1 segment occlusion.

Conclusion

We measured relative CBV with perfusion MR imaging, and relative CBF with SPECT in patients with acute unilateral middle cerebral artery occlusion. The best cutoff values of relative CBV and relative CBF to discriminate between regions with and without evolving infarction were provided with high accuracy. Relative CBV was slightly superior to relative CBF in predicting tissue outcome, although there was no statistically significant difference between the two parameters. For establishment of definite criteria for these perfusion parameters to predict the tissue outcome, further studies with a greater number of patients including those with successful thrombolytic therapy are needed.

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대한자기공명의과학회지 6:55-63(2002)

급성 허혈성 뇌졸중에서 관류 자기공명영상과 99mTC-HMPAO 단광자방출단층촬영술을 이용한 뇌경색의 예측

경상대학교 의과대학 진단방사선과학교실

최 호 철 · 이 선 주 · 김 재 형

목적 : 급성 허혈성 뇌졸중에서 관류 MR영상으로 측정한 상대적 뇌혈용적과 단광자방출전산화단층촬영으로 측정한 상대적 뇌혈류량이 나중에 발생할 뇌경색을 예측할 수 있는 지 알아보고자 하였다.

대상 및 방법 : 급성 일측성 중대뇌동맥 폐색 환자에서 증상 발생 6시간 이내에 관류 MR영상과 99mTc-HMPAO 단광자방출전산화단층촬영을 모두 시행한 13명을 대상으로 하였다. 동맥 폐색에 의한 허혈 부위와 반대측 정상 부위에서 각 관류 변수를 측정하여 그 비(허혈 부위 관류변수 값 / 정상 부위 관류 변수 값)를 구한 후, 나중에 경색으로 이행할 부위와 그렇지 않을 부위를 판별할 수 있는 관류변수 비의 절단값을 계산하였다.

결과 : 경색으로 이행한 부위와 그렇지 않은 부위에서 상대적 뇌혈용적 비의 평균값은 각각 0.58±0.27 and 0.99±0.17 ($p < 0.001$)이었고, 상대적 뇌혈류량 비의 평균 값은 0.41±0.22 and 0.71±0.14 ($p < 0.001$)이었다. 경색으로 이행할 부위와 그렇지 않을 부위를 판별하는 절단값은 상대적 뇌혈용적 비가 0.80, 상대적 뇌혈류량 비가 0.56이었다. 각 절단값의 민감도, 특이도, 능률은 뇌혈용적 비가 80.6, 87.5, 82.7%이었고 상대적 뇌혈류량 비가 72.2, 75.0, 73.0%이었다 (두 관류변수 사이에서 $p > 0.05$).

결론 : 급성 허혈성 뇌졸중에서 상대적 뇌혈용적과 상대적 뇌혈류량의 측정은 뇌경색의 발생을 예측하는 데에 유용한 것으로 사료된다.

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