Annals of Nuclear Medicine Vol. 14, No. 1, 47–52, 2000

Usefulness of cerebral blood flow (CBF) measurements to predict the functional outcome for rehabilitation in patients with cerebrovascular disease (CVD)

Fumihiko TAMAMOTO,* Yukiharu SUMI,** Atsushi NAKANISHI,* Katsuhiko OKAYASU,* Tadayuki MAEHARA*** and Hitoshi KATAYAMA***

*Department of Radiology, Tokyo Metropolitan Ohtsuka Hospital
**Department of Radiology, Juntendo Urayasu Hospital
***Department of Radiology, Juntendo University School of Medicine

Purpose: The objectives of this study were to (1) elucidate the relationship between the mean CBF in the whole brain (Av.mCBF) before rehabilitation of CVD patients and the BI score before and after rehabilitation, (2) determine whether the efficacy of rehabilitation can be predicted by measurement of the Av.mCBF, and (3) investigate what part of the brain was most important to improving the BI score.
Materials and Methods: The Av.mCBFs in 160 patients with CVD were calculated by Patlak plots with ^{99m}Tc-HMPAO before rehabilitation, and we determined the BI score before and after rehabilitation. Based on the BI scores before and after rehabilitation, patients were divided into four groups: Group A, BI = 100; Group B, $80 \leq BI \leq 99$; Group C, $60 \leq BI \leq 79$; Group D, $0 \leq BI \leq 59$. We evaluated the relationship between the Av.mCBF and BI score before and after rehabilitation.
Results: The Av.mCBF before rehabilitation showed a tendency to be more correlated with the BI score after rehabilitation ($r = 0.414$, $p < 0.0001$) than before rehabilitation ($r = 0.272$, $p = 0.0006$). After rehabilitation, there was a tendency for the Av.mCBF value to increase in direct proportion to the BI score of the group: it was highest in Group A and lowest in Group D. The strongest correlation was found between the frontal lobe regional CBF before rehabilitation and the BI score after rehabilitation ($r = 0.343$, $p < 0.0001$).
Conclusions: Measurement of the Av.mCBF before rehabilitation of CVD patients will permit prediction of the efficacy of rehabilitation. Also the regional CBF of the frontal lobe is most important for improving the BI score.

Key words: ^{99m}Tc-HMPAO, cerebral blood flow, SPECT, cerebrovascular disease, rehabilitation

INTRODUCTION

IN RECENT YEARS there has been striking improvement in the survival of patients with acute cerebrovascular disease (CVD). There has therefore been increased interest in the social rehabilitation of the patients and in the functional outcome. Accordingly, attempts have been made to predict in advance the social rehabilitation, functional outcome and independence of CVD patients who have survived the acute phase of the disease. As one such attempt, in the present study we have focused on the rehabilitative efficacy and cerebral blood flow (CBF). We have employed CBF scintigraphy to elucidate the relationship between the CBF and the Barthel Index (BI) score,[1,2] used as an objective indicator of the patients' independence as a result of rehabilitation. We have also investigated the clinical significance of CBF measurement by CBF scintigraphy in relation to the efficacy of rehabilitation.

Objectives

This study had three objectives. One objective was to elucidate the relationship between the mean CBF in the

Received May 19, 1999, revision accepted November 25, 1999.

For reprint contact: Fumihiko Tamamoto, M.D., Department of Radiology, Tokyo Metropolitan Ohtsuka Hospital, 2–8–1 Minami-Ohtsuka, Toshima-ku, Tokyo 170–0005, JAPAN.

whole brain before rehabilitation of CVD patients and the BI score before and after rehabilitation. The second objective was to determine, on the basis of the elucidated relationship, whether or not it was possible to predict the efficacy of rehabilitation by measurements of the whole brain CBF. Finally, the third objective was to investigate the local CBF and the BI score after rehabilitation, and thereby identify the region of the brain whose CBF exerts the greatest effect on rehabilitation.

Patients and Methods (Table 1, Figs. 1, 2)
During the two-year period from March 1995 to March 1997, 160 patients underwent rehabilitation for CVD at Tokyo Metropolitan Otsuka Hospital. They had no history of previous CVD. These patients consisted of 93 cases of ischemic CVD and 67 cases of hemorrhagic CVD. There were 79 males and 81 females, with an age range of 14 to 83 years and a mean age of 61.0 years. The time interval from the onset of CVD until the performance of CBF scintigraphy showed a range of 20 to 240 days, with the mean interval being 81.6 days. The duration of continuous rehabilitation in these patients showed a range of 14 to 231 days, and a mean of 87.9 days. Each of these patients underwent physical therapy, occupational therapy and speech therapy, and the activity of daily living (ADL) was evaluated in terms of the BI score before and after the rehabilitation.

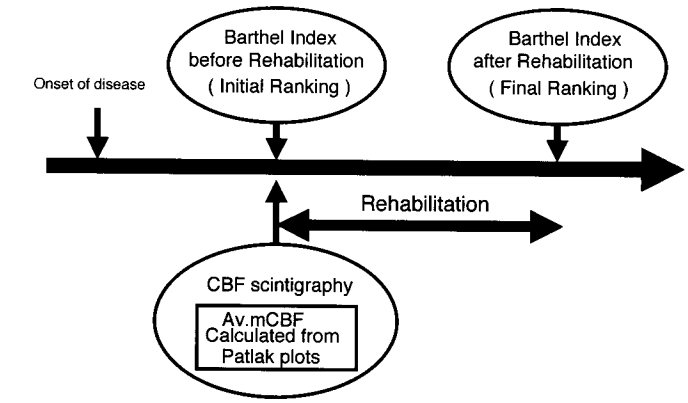
Table 1 Pathology and affected regions

	Number of the CVD	
Cortex	56	
frontal		38
parietal		14
temporal		4
occipital		0
Basal ganglia	70	
caudate		1
putamen		44
thalamus		25
White matter	19	
Cerebellum	4	
Brain stem	11	
Total	160	

CVD: cerebrovascular disease

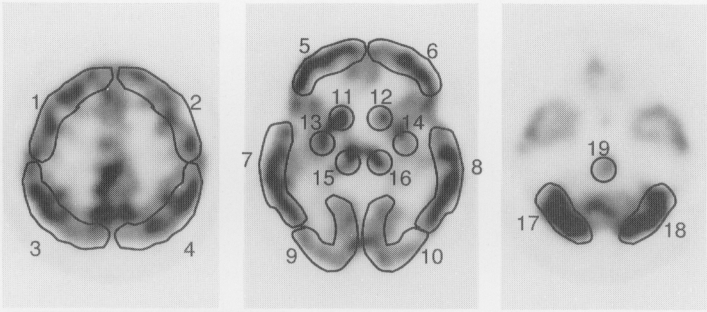
The evaluation of the CBF was done according to the method of Matsuda et al.[3,4] Briefly, prior to the start of rehabilitation, CBF scintigraphy was done with technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO). Then the method of Matsuda et al. was employed to measure the average mean CBF (Av.mCBF) and the regional CBF (rCBF). Dynamic data were collected for 110 seconds at one frame/second with a model GCA-901A Toshiba gamma camera, with 555 MBq of ^{99m}Tc-HMPAO administered by bolus infusion via the right cubital vein (within 20 seconds) with the patient's eyes closed. The Av.mCBF was determined from the bilateral mean CBF (mCBF) as the average of the mCBF values for the right and left hemispheres. The rCBF was also calculated as in Figure 2.

After the collection of the dynamic data, an additional dose of 555 MBq of ^{99m}Tc-HMPAO was administered, and scanning was performed with a model GCA-9300/DI Toshiba three-head rotating gamma camera. SPECT data collection was carried out with an energy window width of 140 keV ± 10%, for a total of 10 rotations, at one rotation/2 minutes with a 128 × 128 matrix. Image reconstruction was performed with a GMS-5500 A/DI and a Butterworth filter as a pretreatment filter, and a Ramp filter was used as the reconstruction filter. Attenuation correction was carried out by the method of Chang et al. with $\mu = 0.08$ and a slice thickness of 3.4 mm. The spatial resolution of the same system was 7.3 mm (FWHM) at a rotational diameter of 13.2 cm. Three slices parallel to the canto-mental line, which include the centrum semiovale, basal ganglia and cerebellum, were selected for rCBF measurement by the method of Matsuda et al.[3,4] Regions of interest (ROIs) were outlined on the frontal lobe,



CBF : cerebral blood flow; Av.mCBF : average mean cerebral blood flow; mCBF : mean cerebral blood flow.
Av.mCBF is defined as (mCBF of the right cerebral hemisphere + mCBF of the left cerebral hemisphere) / 2

Fig. 1 Schematic view of the study protocol.



1: right upper frontal	10: left occipital
2: left upper frontal	11: right caudate N.
3: right parietal	12: left caudate N.
4: left parietal	13: right putamen
5: right lower frontal	14: left putamen
6: left lower frontal	15: right thalamus
7: right temporal	16: left thalamus
8: left temporal	17: right cerebellum
9: right occipital	18: left cerebellum

rCBFs are defined as;

rCBF of the frontal lobe: (1+2+5+6)/ 4
rCBF of the temporal lobe: (7+8)/ 2
rCBF of the parietal lobe: (3+4)/ 2
rCBF of the occipital lobe: (9+10)/ 2
rCBF of the basal ganglia: (11+12+13+14+15+16)/ 6
rCBF of the cerebellum: (17+18)/ 2
rCBF of the brain stem: 19

rCBF: regional cerebral blood flow

Fig. 2 Schemes of ROIs for rCBF on the brain SPECT.

Table 2 Changes in the rankings and Av.mCBF of the groups

	Final Ranking					
	A	B	C	D	Total	
A	*4* 43.6 ± 4.4				*4* 43.6 ± 4.4	Initial Ranking
B	*18* 41.2 ± 7.2	*5* 35.4 ± 5.1			*23* 39.9 ± 7.1	
C	*16* 40.8 ± 5.1	*18* 37.0 ± 3.5	*5* 33.1 ± 2.0		*39* 38.1 ± 4.8	
D	*6* 40.0 ± 4.1	*39* 39.0 ± 5.6	*21* 36.3 ± 5.1	*28* 35.0 ± 4.3	*94* 37.3 ± 5.3	
Total	*44* 41.1 ± 5.8	*62* 38.2 ± 5.1	*26* 35.7 ± 4.8	*28* 35.0 ± 4.3		

Av.mCBF: average mean cerebral blood flow. Data are mean ± standard deviation (m*l*/100 g/min).
Italics show the number of patients in the groups.

parietal lobe, temporal lobe, occipital lobe, basal ganglia, white matter, cerebellum and brain stem, and their rCBFs were estimated.

The effectiveness of rehabilitation was judged by a physician specialized in rehabilitation on the basis of the change in the BI score from before to after rehabilitation. The BI score was corrected according to the method reported by Granger et al. in 1979.[2] Based on the BI scores before and after rehabilitation, the patients were divided into four groups: Group A had a BI score of 100 (the patients are totally recovered and independent), Group B had a BI score within the 80 to 99 range (the patients are able to walk and be independent), Group C had a BI score within the 60 to 79 range (the patients are independent but use a wheelchair), and Group D had a BI score within the 0 to 59 range (the patients are dependent).

Statistical analysis was carried out with the StatView (Abacus Concepts) software. The correlation between the BI and the Av.mCBF was investigated with Spearmann's rank correlation coefficient. Differences in the value of the mean Av.mCBF among the patient groups were tested for statistical significance by one-way ANOVA and the post-hoc test (Fisher's PLSD).

RESULTS

1. Classification of Patients Based on BI Score Prior to Rehabilitation (Table 2)

Prior to rehabilitation, four patients were classified in Group A (BI = 100), and their mean Av.mCBF was 43.6 ± 4.4 m*l*/100 g/min. Similarly, 23 patients were classified in Group B (80 ≤ BI ≤ 99), and their mean Av.mCBF was 39.9 ± 7.1 m*l*/100 g/min, 39 patients were classified in Group C (60 ≤ BI ≤ 79), and their mean Av.mCBF was 38.1 ± 4.8 m*l*/100 g/min, and 94 patients were classified in Group D (0 ≤ BI ≤ 59), and their mean Av.mCBF was 37.3 ± 5.3 m*l*/100 g/min.

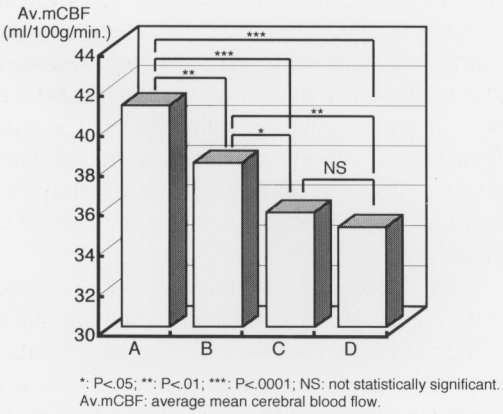


Fig. 3 Av.mCBF in the final rankings after rehabilitation.

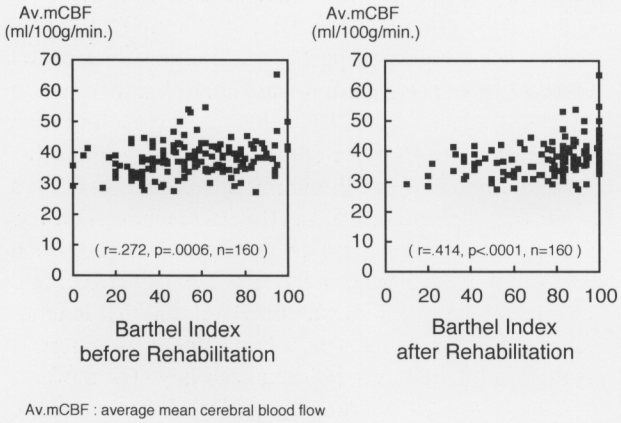


Fig. 4 Overall relationship between Av.mCBF and Barthel index after rehabilitation.

2. Classification of Patients Based on BI Score after Rehabilitation (Table 2, Figs. 3, 4)

After rehabilitation, 44 patients were classified in Group A (BI = 100), and their mean Av.mCBF was 41.1 ± 5.8 m*l*/100 g/min. Similarly, 62 patients were classified in Group B (80 ≤ BI ≤ 99), with a mean Av.mCBF of 38.2 ± 5.1 m*l*/100 g/min, 26 patients were classified in Group C (60 ≤ BI ≤ 79), with a mean Av.mCBF value of 35.7 ± 4.8 m*l*/100 g/min, and 28 patients were classified in Group D (0 ≤ BI ≤ 59), with a mean Av.mCBF value of 35.0 ± 4.3 m*l*/100 g/min. Among these patient groups statistically significance was tested by one-way ANOVA (F-value: 10.208, degrees of freedom (df): 3, p-value: < 0.001). Significant differences were found in the mean Av.mCBF between each two groups except groups C and D (post-hoc test; Fisher's PLSD) (Fig. 3).

3. Relationship between Av.mCBF and BI Score

The Av.mCBF determined before rehabilitation showed a tendency to be more correlated with the BI score after rehabilitation ($r = 0.414$, $p < 0.0001$) than with the BI score before rehabilitation ($r = 0.272$, $p = 0.0006$) (Fig. 4).

Table 3 Spearmann's rank correlation coefficient between rCBF and BI score after rehabilitation

region	r-value	p-value
frontal lobe	0.343	<0.0001
temporal lobe	0.287	0.0002
parietal lobe	0.216	0.0046
occipital lobe	0.156	0.0366
basal ganglia	0.308	0.0002
white matter	0.238	0.0020
cerebellum	0.125	0.0902
brain stem	0.098	0.1768

rCBF: regional cerebral blood flow; BI: Barthel Index; $p < 0.001$

4. Relationship between rCBF of Individual Region and the BI Score after Rehabilitation (Table 3)

The strongest correlation was found between the frontal lobe rCBF before rehabilitation and the BI score after rehabilitation ($r = 0.343$, $p < 0.0001$). And correlation was also found between temporal lobe rCBF ($r = 0.287$, $p = 0.0002$), rCBF of the basal ganglia ($r = 0.308$, $p = 0.0002$) and the BI score after rehabilitation.

DISCUSSION

Numerous attempts have been made to predict the outcome of CVD patients on the basis of the findings of CBF scintigraphy, but most such studies have focused on the survival prognosis during the acute stage of the disease, and many have dealt with the functional outcome during the subsequent chronic stage. Conversely, there have been few studies which carried out a thorough study of patients who underwent rehabilitation. In the present study we employed the Barthel Index (BI) to objectively evaluate the efficacy of rehabilitation of CVD patients. In addition, by the method of Matsuda et al., we achieved quantitative measurement of the Av.mCBF and the rCBF, and we were able to demonstrate a clear correlation between Av.mCBF before rehabilitation and the BI score after rehabilitation. Finally we investigated whether or not these parameters are useful for predicting the efficacy of rehabilitation of CVD patients.

To date there have been several reports of attempts to predict the functional outcome of CVD patients on the basis of the findings of CBF scintigraphy. The methods employed to predict the functional outcome by means of CBF scintigraphy include (I) a method in which SPECT images are prepared by using a tracer such as HMPAO, and then the blood flow defect volume is calculated from those SPECT images, (II) a method which uses N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) and determines the presence/absence and extent of redistribution images, and (III) a method such as the one we employed, in which the Av.mCBF and the rCBF are quantitatively determined.

Limburg et al.[5] employed the first method noted above,

in which the blood flow defect volume is calculated. They reported that they carried out SPECT with ^{201}Tl-diethyldithiocarbamate and found that the blood flow defect at 24 hours after onset of CVD negatively correlated with the functional outcome. In addition, by using the same method of obtaining SPECT images except that the tracer was HMPAO, Lees et al.,[6] Weir et al.,[7] Bowler et al.,[8] Laloux et al.[9] and Davis et al.[10] each found that the volume of the blood flow defect on the SPECT images showed a negative correlation with the patient's functional outcome.

The second CBF scintigraphy method noted above, in which IMP is employed and the presence/absence and extent of redistribution images are determined and used for predicting the functional outcome of CVD patients, was applied by Rupright et al.,[12] Defer et al.[13] and Raynaud et al.[14] These investigators reported that there was a correlation between the extent of redistribution images determined by CBF scintigraphy and the functional outcome.

The method for calculating the cerebral blood flow defect volume has various flaws, including (I) the possibility that, depending on the time of performance of the scintigraphy, the volume of the defect will be greatly altered due to remote effects, luxury perfusion, etc., (II) the possibility that a defect in the rCBF will be overlooked because it cannot be clearly recognized as a defect, and thus, (III) there is a strong possibility that this method will not be useful in the case that there is a diffuse decrease in the blood flow in the whole brain. In addition, the prediction method based on the presence/absence and extent of IMP redistribution images is also considered to involve various problems, including (I) a considerable amount of time is taken for the examination since one examination requires two SPECT imaging procedures, and this can also involve the trouble of moving the patient and (II) there is no way of guaranteeing that the images obtained in the two SPECT procedures represent the same slices.

On the other hand, in 1977 Weiss et al.[15] employed two-dimensional Xenon-133 (^{133}Xe) and applied the third CBF scintigraphic method noted above for predicting the functional outcome of CVD patients, in which the Av.mCBF and the rCBF are quantitatively determined. They found a positive correlation between the CBF and the clinical symptoms, thus indicating the possibility that CBF measurement is useful for predicting the functional outcome of CVD patients. Measurements of the CBF with ^{133}Xe can be carried out repeatedly, and this is also an excellent quantitative method, but it requires puncture of the carotid artery and infusion of an ^{133}Xe gas solution, and it is therefore difficult to consider this to be a safe method in the case of CVD patients and other patients with arteriosclerosis or infarction.

The method we employed for measurement of Av.mCBF and rCBF was originally proposed by Matsuda et al.[3,4] Advantages of this method are that its reproducibility and usefulness have already been established, it is only a mildly noninvasive procedure, and there is no need to collect blood samples. In our institution, we measured the CBF of 29 normal human subjects and found that the data were in good agreement with the CBF data reported by Matsuda et al.,[3,4] and for this reason we are confident that the data generated in our institution are fully reliable for performing accurate evaluation of the CBF of CVD patients.

In the data generated with this method in our present study, the Av.mCBF value before rehabilitation showed a stronger tendency to correlate with the post-rehabilitation BI score than with the pre-rehabilitation BI score in each of the patients studied. And the rCBF of the frontal lobe showed the strongest correlation with the post-rehabilitation BI score. Furthermore, when the CVD patients were classified into four groups (Group A: BI = 100; Group B: $80 \leq BI \leq 99$; Group C: $60 \leq BI \leq 79$; Group D: $0 \leq BI \leq 59$) on the basis of their post-rehabilitation BI score and the results were analyzed, it was found that there was a tendency for the Av.mCBF value to increase in direct proportion to the BI score of the group. We surmise that these findings indicate the importance of frontal blood flow in the manifestation of an effect of rehabilitation. The frontal lobe cortex includes the primary motor cortex and also the premotor region, and the prefrontal area, etc., and our present findings indicate the likelihood that maintenance of the blood flow to these brain regions is important for manifestation of rehabilitation efficacy. The prefrontal area in particular comprises a large portion of the frontal lobe, and there is the possibility that such psychological factors as the patient's volition, etc., influence the efficacy of rehabilitation. In fact, in patients with hemiplegia, although few cases show marked improvement in the symptoms of paralysis from before to after rehabilitation, many cases show improvement in the outcome in terms of the ADL. Such cases indicate that the efficacy of rehabilitation cannot be explained merely on the basis of the improvement in motor functions alone.

Because recovery of function after central nervous system lesions can continue for months or years after injury, the condition in the early phase of the disease does not always decide the functional outcome of the patient. Sprouting: collateral sprouting from intact cells to a denervated region after some or all of its normal input has been destroyed, and Unmasking: the unmasking of neuronal pathways and synapses which are not normally used for a particular function under study but which can be called upon when the ordinary dominant system fails, are considered two major causes of functional recovery in rehabilitation.[11] Effective rehabilitation might promote and stimulate these two mechanisms. Our data suggest that CBF plays an important role in these mechanisms.

In 1997 Rupright et al.[12] employed IMP and attempted to evaluate the efficacy of rehabilitation in patients with cerebral infarction. They reported a correlation between

Table 4 Sensitivity and specificity of positive outcome when cut-off point is 35.0 ml/100 g/min

Functional outcome	Av.mCBF	
	>35.0 ml/ 100 g/min	<35.0 ml/ 100 g/min
good = independent (BI after rehabilitation ≥60)	97	35
poor = dependent (BI after rehabilitation <60)	15	13
Sensitivity	Specificity	Overall accuracy
0.735	0.464	0.688

BI: Barthel Index; Av.mCBF: average mean cerebral blood flow

the extent of IMP redistribution and the Functional Independent Measure (FIM) score. The FIM score is also superior to the BI score for evaluation of the higher level brain functions, such as the psychological factors, etc., and there is the possibility that combined study of the FIM score and the quantitative values for CBF may yield even more useful information.

Our present study is handicapped by a number of problems which include the following: (I) Consideration was not given to the effects of drugs which had been administered to the patients to treat the CVD prior to their admission to our hospital. (II) The duration from the onset of the CVD until the CBF measurement varied greatly, and the degree of recovery from the CVD also varied at the time of the SPECT study. And (III) when the patients were classified into a good functional outcome group and a poor functional outcome group on the basis of the BI score, and an Av.mCBF value of 35.0 ml/100 g/min was employed as the cut-off point, the specificity for the diagnosis of the patient's status (dependent or independent) after rehabilitation was rather low (sensitivity: 0.735; specificity: 0.464; overall accuracy: 0.688) (Table 4).

We think that accurate prediction of the efficacy of rehabilitation will be useful for drawing up the rehabilitation protocol for each individual patient, revision of the protocol, education of the patient's family and helpers, etc., and will make it possible to carry out the rehabilitation in a rational and efficient manner.

CONCLUSIONS

1. The Av.mCBF measured prior to rehabilitation showed a tendency to correlate more closely with the BI score after rehabilitation than with the BI score before rehabilitation.

2. Quantification of the rCBF revealed that the rCBF of the frontal lobe showed the strongest correlation with the BI score after rehabilitation.

3. Accordingly, measurement of the Av.mCBF prior to rehabilitation of CVD patients will permit prediction of the efficacy of rehabilitation of the individual patient, and it will also make it possible to carry out the rehabilitation in a rational and efficient manner.

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