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

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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 99mTc-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 ≤ BI ≤ 99; Group C, 60 ≤ BI ≤ 79; Group D, 0 ≤ BI ≤ 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: 99mTc-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,12 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
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.

The evaluation of the CBF was done according to the method of Matsuda et al.\(^4\) 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 (\(\text{Av}_{m}\text{CBF}\)) 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 \(\text{Av}_{m}\text{CBF}\) 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.\(^4\) Regions of interest (ROIs) were outlined on the frontal lobe.

**Table 1** Pathology and affected regions

<table>
<thead>
<tr>
<th></th>
<th>Number of the CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>56</td>
</tr>
<tr>
<td>frontal</td>
<td>38</td>
</tr>
<tr>
<td>parietal</td>
<td>14</td>
</tr>
<tr>
<td>temporal</td>
<td>4</td>
</tr>
<tr>
<td>occipital</td>
<td>0</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>70</td>
</tr>
<tr>
<td>caudate</td>
<td>1</td>
</tr>
<tr>
<td>putamen</td>
<td>44</td>
</tr>
<tr>
<td>thalamus</td>
<td>25</td>
</tr>
<tr>
<td>White matter</td>
<td>19</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>4</td>
</tr>
<tr>
<td>Brain stem</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
</tr>
</tbody>
</table>

CVD: cerebrovascular disease

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**Fig. 1** Schematic view of the study protocol.
Fig. 2 Schemes of ROIs for rCBF on the brain SPECT.

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

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>4</td>
<td>18</td>
<td>16</td>
<td>4</td>
<td>43.6 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>43.6 ± 4.4</td>
<td>5</td>
<td>37.0 ± 3.5</td>
<td>5</td>
<td>39.9 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>35.4 ± 5.1</td>
<td>41.2 ± 7.2</td>
<td>33.1 ± 2.0</td>
<td>38.1 ± 4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>39</td>
<td>28</td>
<td>37.3 ± 5.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>62</td>
<td>26</td>
<td>35.0 ± 4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41.1 ± 5.8</td>
<td>38.2 ± 5.1</td>
<td>35.7 ± 4.8</td>
<td>35.0 ± 4.3</td>
<td></td>
</tr>
</tbody>
</table>

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

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. 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 ml/100 g/min. Similarly, 23 patients were classified in Group B (80 ≤ BI ≤ 99), and their mean Av.mCBF was 39.9 ± 7.1 ml/100 g/min. 39 patients were classified in Group C (60 ≤ BI ≤ 79), and their mean Av.mCBF was 38.1 ± 4.8 ml/100 g/min, and 94 patients were classified in Group D (0 ≤ BI ≤ 59), and their mean Av.mCBF was 37.3 ± 5.3 ml/100 g/min.
Table 3 Spearman’s rank correlation coefficient between rCBF and BI score after rehabilitation

<table>
<thead>
<tr>
<th>region</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal lobe</td>
<td>0.343</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>0.287</td>
<td>0.0002</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>0.216</td>
<td>0.0046</td>
</tr>
<tr>
<td>occipital lobe</td>
<td>0.156</td>
<td>0.0366</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>0.308</td>
<td>0.0002</td>
</tr>
<tr>
<td>white matter</td>
<td>0.238</td>
<td>0.0020</td>
</tr>
<tr>
<td>cerebellum</td>
<td>0.125</td>
<td>0.0902</td>
</tr>
<tr>
<td>brain stem</td>
<td>0.098</td>
<td>0.1768</td>
</tr>
</tbody>
</table>

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 HMPOAO, and then the blood flow defect volume is calculated from those SPECT images, (II) a method which uses N-isopropyl-p-[113I]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,

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in which the blood flow defect volume is calculated. They reported that they carried out SPECT with $^{201}$Tl-diethyl-
dithiocarbamate 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., Weir et al., Bowler et al., Laloux et al. and Davis et al. 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,
as applied by Rupright et al., Defer et al. and Raynaud
et al. These investigators reported that there was a
relation 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
cintigraphy, 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. employed a
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. Advantages of this method are that its reproduc-
ibility 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. 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-rehabilite-
ration BI score. Furthermore, when the CVD patients were
classified into four groups (Group A: BI = 100; Group B:
80 ≤ BI ≤ 99; Group C: 60 ≤ BI ≤ 79; Group D: 0 ≤ BI ≤ 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 mainte-
nance of the blood flow to these brain regions is important
for manifestation of rehabilitation efficacy. The prefront-
oral area in particular comprises a large portion of the
frontal lobe, and there is the possibility that such psycho-
logical factors as the patient’s volition, etc., influence
the efficacy of rehabilitation. In fact, in patients with hemi-
plegia, 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 rehabili-
tation 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 neu-
ronal 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. 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. applied 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

<table>
<thead>
<tr>
<th>Functional outcome</th>
<th>Av mCBF &gt;35.0 ml/100 g/min</th>
<th>Av mCBF &lt;35.0 ml/100 g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>good = independent</td>
<td>97</td>
<td>35</td>
</tr>
<tr>
<td>(BI after rehabilitation ≥60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>poor = dependent</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>(BI after rehabilitation &lt;60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.735</td>
<td>0.464</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.464</td>
<td>0.688</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

REFERENCES


